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Contract No.: DAMD17-92-C-2001
Task Order No.: UIC-13D
Study No.: 173

Title Page

Study Report for Task Order No. UIC-13D

DEVELOPMENTAL TOXICITY (SEGMENT II)
STUDY OF WR6026 DIHYDROCHLORIDE IN RABBITS

Sponsor: U.S. Army Medical Materiel
Development Activity

Test Article: WR6026 DIHYDROCHLORIDE

Contract No.: DAMD17-92-C-2001

Study Director

Barry S. Levine, D.Sc., D.A.B.T.

In-Life Phase Completed On

April 7, 1995

Performing Laboratory

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SECURITY CLASSIFICATION OF THIS PAGE

REPORT DOCUMENTATION PAGE

Form Approved
OMB No. 0704-0188

1a. REPORT SECURITY CLASSIFICATION			1b. RESTRICTIVE MARKINGS		
2a. SECURITY CLASSIFICATION AUTHORITY Unclassified			3. DISTRIBUTION/AVAILABILITY OF REPORT Unlimited		
2b. DECLASSIFICATION/DOWNGRADING SCHEDULE					
4. PERFORMING ORGANIZATION REPORT NUMBER(S) UIC-13D (UIC/TRL Study No. 173)			5. MONITORING ORGANIZATION REPORT NUMBER(S)		
6a. NAME OF PERFORMING ORGANIZATION Toxicology Research Laboratory University of Illinois at Chicago		6b. OFFICE SYMBOL (If applicable)	7a. NAME OF MONITORING ORGANIZATION U.S. Army Medical Materiel Development Activity		
6c. ADDRESS (City, State, and ZIP Code) Department of Pharmacology (M/C 868) 1940 W. Taylor Street Chicago, IL 60612-7353			7b. ADDRESS (City, State, and ZIP Code) ATTN: MCMR-RMA-RD Fort Detrick Frederick, MD 21702-5014		
8a. NAME OF FUNDING/SPONSORING ORGANIZATION U.S. Army Medical Materiel Development Activity		8b. OFFICE SYMBOL (If applicable) MCMR-UMP	9. PROCUREMENT INSTRUMENT IDENTIFICATION NUMBER DAMD17-92-C-2001		
8c. ADDRESS (City, State, and ZIP Code) Fort Detrick Frederick, MD 21702-5009			10. SOURCE OF FUNDING NUMBERS		
			PROGRAM ELEMENT NO. 63807A	PROJECT NO. 30463807	TASK NO. QC
			WORK UNIT ACCESSION NO. 073		
11. TITLE (Include Security Classification) Developmental Toxicity (Segment II) Study of WR6026 Dihydrochloride in Rabbits					
12. PERSONAL AUTHOR(S) Levine, B.S., Youssef, A.F. and Mercieca, M. (PAI)					
13a. TYPE OF REPORT Study		13b. TIME COVERED FROM _____ TO _____		14. DATE OF REPORT (Year, Month, Day)	
15. PAGE COUNT					
16. SUPPLEMENTARY NOTATION					
17. COSATI CODES			18. SUBJECT TERMS (Continue on reverse if necessary and identify by block number)		
FIELD	GROUP	SUB-GROUP	Rabbits		
			WR6026 Dihydrochloride		
			Developmental Toxicity		
19. ABSTRACT (Continue on reverse if necessary and identify by block number)					
<p>This study evaluated the developmental toxicity of WR6026 Dihydrochloride in time-mated New Zealand White (Pasteurella Free) female rabbits. Doses were 0, 3, 7, and 15/10 mg base/kg/day administered by gavage during gestation days (GD) 6 - 18 (GD0 = day of observed mating). The high dose was reduced from 15 mg base/kg/day to 10 mg base/kg/day on gestation days 12 - 15 due to the death of four animals (the range of days reflects the study stagger-start over four days). A positive control group was administered retinol palmitate, 300 mg/kg/day, on GD9, and GD10 or GD12 (in 5 females) by gavage. Toxic manifestations were only seen in the high dose group, and included an increase in respiratory rate associated with cyanosis. No biologically significant decreases in body weight/weight gain or in food consumption were observed at the high dose following dose level reduction. Ten mg base/kg/day was therefore considered at or near the maternal NOEL. This observation is supported by the results of a previously conducted dose range-finding study (UIC/TRL Study No. 172) in which no effects were seen at 10 mg base/kg/day, whereas maternal mortality occurred at 20 mg base/kg/day. Females in the positive control group did not show any significant drug-related effects. At the 15/10 mg base/kg/day level, two litters were observed with fetuses having vertebral anomalies. No statistically significant increases in the number of litters with skeletal malformations resulted. However, since the malformations observed for the fetuses from both litters were of a similar nature, it is unclear if the vertebral anomalies were or were not a result of treatment with WR6026 Dihydrochloride at 15/10 mg base/kg/day (a maternally lethal dose level). Accordingly, 7 and possibly 15/10 mg base/kg/day was considered at or near the NOEL dose for developmental toxicity. In a previously conducted developmental toxicity study in rats, 2 mg base/kg/day was considered at or near the NOEL for fetal and maternal toxicity (UIC/TRL Study No. 171). Rats therefore demonstrated greater developmental sensitivity to WR6026 Dihydrochloride than rabbits. In the rat teratology study, WR6026 Dihydrochloride did not demonstrate a developmental hazard to rat fetuses except in maternally toxic doses (8 mg base/kg/day). At those dose levels, fetal body weights were reduced, but treatment-related malformations were not observed.</p>					
20. DISTRIBUTION/AVAILABILITY OF ABSTRACT <input type="checkbox"/> UNCLASSIFIED/UNLIMITED <input checked="" type="checkbox"/> SAME AS RPT. <input type="checkbox"/> DTIC USERS			21. ABSTRACT SECURITY CLASSIFICATION Unclassified		
22a. NAME OF RESPONSIBLE INDIVIDUAL Barry S. Levine			22b. TELEPHONE (Include Area Code) (312) 996-5543		22c. OFFICE SYMBOL N/A

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Contract No.: DAMD17-92-C-2001
Task Order No.: UIC-13D
Study No.: 173

STATEMENT OF COMPLIANCE

To the best of my knowledge, Study No. 173 entitled "Developmental Toxicity (Segment II) Study of WR6026 Dihydrochloride in Rabbits" was conducted in compliance with the Good Laboratory Practices regulations as published in 21 CFR 58, 40 CFR 160 and 40 CFR 792 in all material aspects.

The protocol for this study was demonstrated by the UIC Animal Care Committee.

Signature

Study Director

Barry S. Levine, D.Sc., D.A.B.T.

Date

QUALITY ASSURANCE STATEMENT

STUDY TITLE: DEVELOPMENTAL TOXICITY (SEGMENT II) STUDY OF
WR6026 DIHYDROCHLORIDE IN RABBITS

STUDY NUMBER: 173

STUDY DIRECTOR: BARRY S. LEVINE

INITIATION DATE: 7/5/94

This study has been divided into a series of phases. Using a random sampling approach, Quality Assurance personnel monitors each of these phases over a series of studies. Procedures, equipment, documentation, etc., are examined in order to assure that the study is performed in accordance with the Good Laboratory Practice regulations of the Food and Drug Administration and the Environmental Protection Agency to assure that the study is conducted according to the protocol.

The following are the inspection dates, phases inspected, and report dates of QA inspections of the study.

INSPECT ON 7/5/94, TO STUDY DIR 7/5/94, TO MGMT 7/6/94
PHASES: PROTOCOL REVIEW

INSPECT ON 3/7/95, TO STUDY DIR 3/8/95, TO MGMT 3/10/95
PHASES: ANIMAL RECEIPT, ROOM ENVIRONMENT, AND QUARANTINE

INSPECT ON 4/4-5/95, TO STUDY DIR 4/5/95, TO MGMT 4/5/95
PHASES: RAW DATA AND DRAFT REPORT FROM THE ANALYTICAL LABORATORY

INSPECT ON 4/6/95, TO STUDY DIR 4/7/95, TO MGMT 4/10/95
PHASES: EUTHANASIA, CESAREAN-SECTIONING OBSERVATIONS AND FETAL
OBSERVATIONS AND EXAMINATIONS

INSPECT ON 5/30-31/95, TO STUDY DIR 5/31/95, TO MGMT 6/1/95
PHASES: RAW DATA

INSPECT ON 6/20-21/95, TO STUDY DIR 6/21/95, TO MGMT 6/21/95
PHASES: TERATOLOGY DRAFT REPORT

INSPECT ON 6/29/95, TO STUDY DIR 6/29/95, TO MGMT 6/29/95
PHASES: DRAFT REPORT



QUALITY ASSURANCE



DATE

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DEVELOPMENTAL TOXICITY (SEGMENT II)
STUDY OF WR6026 DIHYDROCHLORIDE IN RABBITS

TRL Chemical No.: 1540614

Sponsor: U.S. Army Medical Materiel
Development Activity
Fort Detrick
Frederick, MD 21702-5009

Test Article: WR6026 Dihydrochloride

Sponsor
Representative: George J. Schieferstein, Ph.D.

Testing Facility: TOXICOLOGY RESEARCH LABORATORY (TRL)
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Reproductive Toxicologist

Date

In-life Phase Initiation: March 6, 1995

Dosing Initiation: March 12, 1995

In-Life Completion: April 7, 1995

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1. SUMMARY

This study evaluated the developmental toxicity of WR6026 Dihydrochloride in time-mated New Zealand White (Pasteurella Free) female rabbits. Doses were 0, 3, 7, and 15/10 mg base/kg/day administered by gavage during gestation days (GD) 6 - 18 (GD0 = day of observed mating). The high dose was reduced from 15 mg base/kg/day to 10 mg base/kg/day on gestation days 12 - 15 due to maternal lethality (the range of days reflects study stagger-start over 4 days). A positive control group was administered retinol palmitate, 300 mg/kg/day, by gavage on GD9 and GD10 or GD9 and GD12 (in 5 females). The results are summarized in Table 1. Maternal toxic manifestations were only observed in high dose animals. After four females in the high dose group died during the first several days of treatment, the high dose was reduced to 10 mg base/kg/day. Increases in respiratory rate associated with bluish discoloration of the sclera and ears in some animals were seen for intervals of 1 - 11 days during the dosing period (i.e., GD6 - 18). Statistically significant sporadic reductions in body weight/weight gain and food consumption were observed prior to high dose reduction. No drug-related changes in any maternal reproductive indices were observed. In the previously-conducted dose range-finding study in rabbits (UIC/TRL Study No. 172), no maternal toxicity was observed at 10 mg base/kg/day although mortality did occur at the 20 mg base/kg/day dose level.

No evidence of developmental toxicity was observed at the 3 and 7 mg base/kg/day levels. Teratologic results at the maternally lethal dose of 15/10 mg base/kg/day were equivocal as vertebral malformations were observed in two litters, the incidence of which was not statistically significant. The no-effect level for developmental toxicity of WR6026 Dihydrochloride in rabbits was at least 7 mg base/kg/day and possibly 15/10 mg base/kg/day.

Females in the positive control group did not show any toxic manifestations, however, biologically marginal decreases in the number of viable fetuses resulted from statistically significant increases in the number of early resorptions, % post implantation loss and % total loss/litter. Significant increases in the incidence of external, visceral and skeletal malformations were also noted in these litters.

2. INTRODUCTION

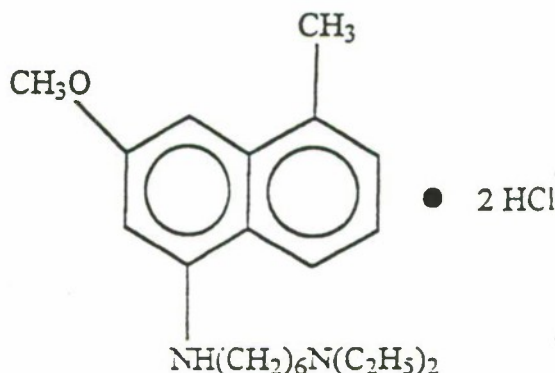
This study was conducted to evaluate the developmental toxicity of the test article in New Zealand white rabbits. The test article was administered by daily gavage to time-mated females during gestation days 6 - 18. The fetuses were delivered by Cesarean section on gestation day 29. All fetuses were examined for external anomalies and by Staples' technique for visceral anomalies, then fixed in ethyl alcohol (95%) for subsequent skeletal examinations. All methods and procedures in this study were conducted in accordance with the Toxicology Research Laboratory, University of Illinois at Chicago and Pathology Associates Inc. Quality Assurance Programs designed to conform with FDA Good Laboratory Practices Regulations. No unforeseen circumstances affected the integrity of the study. This study was stagger-started over four days and was initiated on March 6, 1994 (observation of mating). Dosing was initiated (stagger-started) on March 12, 1995 (GD6) and the in-life portion was terminated on April 7, 1995 (GD29).

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3. MATERIALS AND METHODS

3.1 Test Article

WR6026 dihydrochloride (Bottle Number BK01845), a light yellow powder, was received in two shipments on December 5, 1995 and December 7, 1995 from Herner & Co., and was previously assigned an in-house chemical number (1540614). The chemical name of the test article is 6-methoxy-8-(6-diethylaminohexylamino)lepidine dihydrochloride and the mole fraction of the base is 0.825. It was stored at -20 to -16°C and the container was kept tightly closed in a desiccator. It was also protected from light (the container was wrapped in aluminum foil). The chemical structure follows.



The test article was initially identified by GC-MS and the purity was determined to be greater than 99.58%. The purity was re-determined following the completion of the in-life portion of the study. At that time, the purity was greater than 99.49%. Thus, the test article was stable under storage conditions.

Vitamin A (Retinol Palmitate, all-trans) was purchased from Sigma Co., St. Louis, MO. It was kept at 0 - 4°C at ambient humidity, and was protected from light in an amber bottle.

3.2 Animals

One-hundred and twenty female New Zealand White (*Pasteurella* Free) rabbits were obtained from HRP, Inc., Denver, PA, on 3/07/95 and 3/10/95 (30 and 90 animals, respectively). The animals were $\approx 5\frac{1}{2}$ to 6 months old upon arrival at the UIC AAALAC-accredited animal facility (dates of birth 09/03/94 and 09/24/94). Each animal was given an ear tag number by the supplier, and a separate study-unique number (ear-tag) upon arrival. This number appeared on a cage card visible on the front of each cage. The cage card additionally contained the study number, test article identification, treatment group number, dose level, and the assigned date of necropsy. Cage cards were color-coded as a function of treatment group. Animals were singly housed in stainless steel cages in a temperature (61 - 69°F) and humidity (30 - 70 %) controlled room with a 14 hour light/10 hour dark cycle. The cage size, 0.32 m² area and 38 cm height, was adequate to house rabbits at the upper weight range as described in the *Guide for the Care and Use of Laboratory Animals*, DHHS (NIH) No. 86.23. All animals were routinely transferred to clean cages every other week with pan changes twice weekly.

The animals were fasted on the day of arrival. They received approximately 25 g of High Fiber Certified Rabbit Chow No.5325 (PMI Feeds, Inc., St. Louis, MO) on the second day, which was gradually increased over a few days to approximately 100-130 g/day. This regimen was recommended by the animal supplier (HRP, Inc.) to reduce the incidence of intestinal problems. On the days of measured food consumption, an exact amount of 130 g was provided. Tap water from an automatic watering system in which the room distribution lines were flushed daily was provided *ad libitum* from arrival until termination. The water was not treated with additional chlorine or HCl. There are no known contaminants in the feed or water which were expected to influence the study. The results of the most current comprehensive chemical analyses of Chicago water performed by the City of Chicago are documented in files maintained by Quality Assurance.

3.3 Experimental Design

Animals were mated on four consecutive days at the supplier's facility. The day of mating was considered gestation day 0 (GD0). The body weights on GD0 were obtained by the supplier after balance standardization. Of the 120 presumed pregnant rabbits which were received, 60, 30 and 30 were at GD1, GD2, and GD3, respectively, upon arrival at the animal facility. All animals were quarantined for at least 3 days before initiation of dosing (GD6). All animals were examined daily during the quarantine period, and were approved for use by the Clinical Veterinarian prior to being placed on test. One hundred animals (25 animals from each gestation day 0 subset) were randomized into the following five groups on the basis of body weight to result in 20 animals/group. Dose levels were selected on the basis of a range-finding study (UIC/TRL Study No. 172) as follows:

<u>Group No.</u>	<u>Treatment</u>	<u>Dose Level (mg base/kg/day)</u>	<u>Number of Females*</u>
1	Vehicle	0	20
2	WR6026•2HCl	3	20
3	WR6026•2HCl	7	20
4	WR6026•2HCl	15/10***	20
5**	Vitamin A (Retinol Palmitate)	75,000 IU/kg/day (300 mg/kg/day)	20

* Presumed pregnant

** The positive control agent was administered orally at the specified dose on gestation days 9 and 10 in deionized distilled water at a dosing volume of 1 ml/kg/day (except for 5 females which were dosed on gestation days 9 and 12) It was prepared fresh on each day, and was dispersed in the vehicle within 30 minutes of initiation of dosing.

*** The high dose was reduced from 15 mg base/kg/day to 10 mg base/kg/day on gestation days 12 - 15 (the range of days reflects study stagger-start over 4 days).

The test article was administered by gavage once daily during gestation days 6 through 18. The dosing solutions were administered at a dosing volume of 1 ml/kg. Each dosage formulation was prepared separately once at the beginning of the study (except for the high dose) by dissolving the appropriate quantity of the test article in the vehicle (deionized distilled water). For the high dose, the dosing solution was reformulated and analyzed when the dose level was reduced from 15 to 10 mg base/kg/day. All dosing solutions were kept at 0 - 4°C.

Samples of the dosage formulations were analyzed prior to use and at the end of the dosing period. Only samples within 10% of their intended concentration were used. Stability data obtained from a previous study (UIC/TRL Study No. 091) indicated that the dosing solutions were stable for at least 12 days.

Non-fasted body weights were recorded on GD0 (by the supplier), GD5 (for randomization), and on GD6 - 18, 24 and 29. Food consumption for all animals was measured during the following 24 hr intervals: GD7/8, 9/10, 11/12, 14/15, 17/18, 23/24 and 28/29. Clinical signs were observed and recorded approximately 1 - 2 hours post-dosing on the days of dosing (GD6 - 18) and each morning following completion of the dosing period (GD19 - 29). Animals were also observed twice daily for moribundity/mortality, immediately prior to dosing and in the afternoon, at least six hours apart, and in the afternoon after completion of the dosing period.

On GD29, all surviving rabbits were killed in random order by intravenous injection of sodium pentobarbital (50 mg/kg) via the marginal ear vein. The abdominal and thoracic cavities were opened by a ventral midline incision, a gross necropsy was performed, and the uterus was examined and weighed.

In gravid animals, the number of *corpora lutea* on each ovary was recorded and the ovaries were discarded after evaluation. The viability of the fetuses was determined *in utero*. A viable fetus was defined as one which responds to stimuli. A non-viable fetus was defined as a term fetus which does not respond to stimuli *in utero* or is not breathing. The number and location of fetuses, early resorption(s), late resorption(s) and the total number of implantation sites and their uterine distribution were documented using the following procedure. All implantation sites, including resorptions, were numbered in consecutive fashion beginning with the left distal uterine horn, and similarly with the right uterine horn noting the position of the cervix. An early resorption was defined as one in which it was not grossly evident that organogenesis has occurred. A late resorption was defined as one in which it was grossly evident that organogenesis had occurred. A fetus with evident autolysis was considered a late resorption. Following the cesarean section examination, the carcass of each dam was discarded. Embryos which were prematurely examined due to maternal death or early sacrifice were described according to the stage of *in utero* development.

Uteri from females that appeared nongravid were opened and placed in 10% ammonium sulfide solution for at least 10 minutes for detection of possible implantation sites. If implantation sites were detected, ovaries were evaluated as previously mentioned.

The number of fetuses in each litter was recorded. Each fetus was weighed and individually identified noting litter, uterine placement and study number. All fetuses were euthanized by ip injection of a 40% solution of sodium pentobarbital (\approx 0.4 ml/fetus). Subsequently, a

morphological examination was performed. A detailed examination of each fetus was conducted to include the eyes, palate, head shape and extremities. Any abnormal finding was recorded.

All fetuses were freshly examined by the Staples' technique for visceral anomalies including a mid-sagittal section between the eyes (Staples, 1974). All fetuses were then skinned and eviscerated. Following staining with Alizarin Red S and then cleared in glycerin as recommended by Dawson, the skeletons were examined for alterations (Dawson, 1926). Skeletal preparations were stored in 99.5% glycerin/0.5% phenol.

3.4 Statistical Analyses:

Maternal body weights, weight gains, absolute uterine weights, and fetal body weights were analyzed by one-way analysis of variance. If a significant F ratio was obtained ($p \leq 0.05$), Dunnett's test was used for pair-wise comparisons to the vehicle control group.

Fetal abnormalities were statistically analyzed in terms of the litter as the experimental unit. Abnormalities included malformations in addition to variations. The proportions of litters with abnormalities were compared using Fisher's exact test. Male to female fetal sex ratios were compared using the Chi-square test.

Maternal food consumption data, early and late resorptions, non-viable fetuses, viable fetuses, *corpora lutea* (C.L.), implantations, preimplantation loss*, postimplantation loss**, and total implantation loss*** were compared using the Kruskal-Wallis test. If a significant effect was seen ($p \leq 0.05$), the Mann-Whitney U test was used for pair-wise comparisons to the vehicle control group.

*Preimplantation loss = $[(\# \text{ C.L.} - \# \text{ implantations})/\# \text{ C.L.}] \times 100$

**Postimplantation loss = $[(\# \text{ implantations} - \# \text{ live fetuses})/\# \text{ implantations}] \times 100$

***Total implantation = $[(\text{C.L.} - \# \text{ live fetuses})/\# \text{ C.L.}] \times 100$

Uterine weight, fetal body weights and fetal sex in animals with abortion/premature delivery were not included in the statistical analysis.

In addition to the written report, summary data tables of parameters and variability were transmitted to the Sponsor on magnetic media (computer diskette) in "ASCII" form. The transcribed data on disk were no longer considered GLP compliant.

4. RESULTS

4.1 Dosage Formulation Analysis

The results of dosage formulation analyses are shown in Table 2. The Analytical Chemistry Report is in Appendix 1.

All dosage formulations were within 10% of their target concentration.

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4.2 Mortality/Clinical Signs

The summary of clinical signs of toxicity is in Table 3. Individual signs are in Appendix 2.

In the high dose (15 mg base/kg/day), 4 females were found dead; one each on GD10, 11, 14 and 15. Accordingly, the dose was reduced to 10 mg base/kg/day. ^{on what day} The majority of the high dose animals demonstrated an increase in respiratory rate which ranged from 1 to 11 days. Cyanosis was also seen in a few high dose animals as evidenced by a bluish discoloration of the ears and sclera. Clinical signs of toxicity were not seen in the lower dose levels. A mid dose female was sacrificed moribund due to a broken back with subsequent deterioration and loss in body weight. Females in the positive control group did not show any manifestations of toxicity.

4.3 Maternal Body Weights

The summaries of maternal body weights and weight gains are in Tables 4 and 5, respectively. Individual data are contained in Appendix 3.

In the high dose, a marginal, but statistically significant decrease in body weight gain was observed on GD12, prior to dose level reduction. This was not seen on other days, and no biologically significant decrease in total weight gain was observed by GD29. In the positive control group, apart from a sporadic, but statistically significant decrease in weight gain on GD24, no changes in bodyweight/weight gain were observed.

4.4 Food Consumption

The summary of mean daily food consumption is in Table 6. Individual food consumption data are contained in Appendix 4.

A statistically significant decrease in food consumption was observed on GD12 and 15 in high dose animals. This was not seen after dose level reduction for these animals. Food intake was not altered in the lower dose levels or in the positive control animals.

4.5 Cesarean-Section and Maternal Gross Observations

The summary of cesarean-section data is in Table 7. The Teratology Report is in Appendix 5.

The pregnancy rate was at least 90% in all groups. No biologically meaningful change was observed in any of the reproductive indices in WR6026 Dihydrochloride-treated animals. A statistically significant increase in the number of viable fetuses in the 3 mg base/kg/day dose group was considered incidental.

In the positive control group, a statistically significant increase in the numbers of early resorptions, % post-implantation loss, and % total loss/litter, and a non-statistically significant decrease in the number of viable fetuses were observed.

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4.6 Fetal Observations

The summary of fetal observation is in Table 7. The Teratology Report is in Appendix 5.

Fetuses of females dosed with WR6026 Dihydrochloride did not show any statistically significant increases in treatment-related malformations or developmental variations. Two litters in the 15/10 mg base/kg/day dose group had fetuses with various vertebral anomalies (e.g., 8th cervical vertebra). These anomalies were not seen in the lower dose levels or in the vehicle control group.

The litters in the positive control group showed statistically significant increases in external, visceral and skeletal malformations. These anomalies were not associated with decreases in fetal body weight.

5. DISCUSSION/CONCLUSION

This study evaluated the embryo/fetal toxicity and the teratogenic potential of WR6026 Dihydrochloride in time-mated New Zealand White (Pasteurella Free) female rabbits. Doses were 0, 3, 7, and 15/10 mg base/kg/day administered by gavage during gestation days (GD) 6 - 18 (GD0 = day of observed mating). The high dose was reduced from 15 mg base/kg/day to 10 mg base/kg/day on gestation days 12 - 15 due to the death of four animals (the range of days reflects the study stagger-start over four days). A positive control group was administered retinol palmitate, 300 mg/kg/day, on GD9, and GD10 or GD12 (in 5 females) by gavage. The results are summarized in Table 1.

Toxic manifestations were only seen in the high dose group, and included an increase in respiratory rate associated with cyanosis. No biologically significant decreases in body weight/weight gain or in food consumption were observed at the high dose following dose level reduction. Ten mg base/kg/day was therefore considered at or near the maternal NOEL. This observation is supported by the results of a previously conducted dose range-finding study (UIC/TRL Study No. 172) in which no effects were seen at 10 mg base/kg/day, whereas maternal mortality occurred at 20 mg base/kg/day. Females in the positive control group did not show any significant drug-related effects.

At the 15/10 mg base/kg/day level, two litters were observed with fetuses having vertebral anomalies. No statistically significant increases in the number of litters with skeletal malformations resulted. However, since the malformations observed for the fetuses from both litters were of a similar nature, it is unclear if the vertebral anomalies were or were not a result of treatment with WR6026 Dihydrochloride at 15/10 mg base/day (a maternally lethal dose level). Accordingly, 7 and possibly 15/10 mg base/kg/day was considered at or near the NOEL dose for developmental toxicity.

In a previously conducted developmental toxicity study in rats, 2 mg base/kg/day was considered at or near the NOEL for fetal and maternal toxicity (UIC/TRL Study No. 171). Rats therefore demonstrated greater developmental sensitivity to WR6026 Dihydrochloride than rabbits. In the rat teratology study, WR6026 Dihydrochloride did not demonstrate a developmental hazard to rat fetuses except in maternally toxic doses (8 mg base/kg/day or greater). At those dose levels, fetal body weights were reduced, but treatment-related malformations were not observed.

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Contract No.: DAMD17-92-C-2001
Task Order No.: UIC-13D
Study No.: 173

6. REFERENCES

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Staples, R.E. (1974). Detection of visceral alterations in mammalian fetuses. Teratol. 9:A-37.

7. PERSONNEL

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Lead Technician	Nancy Dinger, B.S.
Chemistry Specialist	Thomas Tolhurst, B.S.
Quality Assurance	Ronald C. Schoenbeck

Report preparation was assisted by Dr. Ashraf Youssef, Ms. Soudabeh Soura and Mr. Mukesh Pitroda.

8. ARCHIVES

All raw data, documentation, specimens, test article reserves, and the final report are archived at the University of Illinois at Chicago, Toxicology Research Laboratory, Department of Pharmacology, 1940 W. Taylor St., Chicago, IL 60612.

DRAFT

Contract No.: DAMD17-92-C-2001
Task Order No.: UIC-13D
Study No.: 173

Table 1

DEVELOPMENTAL TOXICITY (SEGMENT II) STUDY OF WR6026 DIHYDROCHLORIDE IN RABBITS

Summary of Toxic Responses

	WR6026 Dihydrochloride				Retinol Palmitate
Dose Level (mg base/kg/day)	0	3	7	15/10	300 mg/kg/day*
Number of Females Pregnant (Non-pregnant)	20(0)	18(2)	20(0)	20(0)	19(1)
Term Litters with Early Termination of Pregnancy (cause)	0	0	1 (MS)	4 (FD)	0
Clinical Signs	-	NE	NE	RRJ (14) C (3)	NE
Maternal Body Weight Gain	-	NE	NE	↓?	NE
Food Consumption	-	NE	NE	↓	NE
Uterine Weight	-	NE	NE	NE	NE
Early Resorptions	-	NE	NE	NE	↑
Post-implantation Loss	-	NE	NE	NE	↑
Decrease in Fetal Body Weight (♂/♀)	-	NE/NE	NE/NE	NE/NE	NE/NE
Viable Fetuses	-	NE	NE	NE	↓(?)
Total Loss/Litter	-	NE	NE	NE	↑
External Malformations	-	NE	NE	NE	↑
Skeletal malformations	-	NE	NE	↑?	↑
Visceral Malformations	-	NE	NE	NE	↑
<p>CONCLUSIONS</p> <p>This study evaluated the developmental toxicity of WR6026 Dihydrochloride in time-mated New Zealand White (Pasteurella Free) female rabbits. Doses were 0, 3, 7, and 15/10 mg base/kg/day administered by gavage during gestation days (GD) 6 - 18 (GD0 = day of observed mating). The high dose was reduced from 15 mg base/kg/day to 10 mg base/kg/day on gestation days 12 - 15 due to the death of four animals (the range of days reflects the study stagger-start over four days). A positive control group was administered retinol palmitate, 300 mg/kg/day, on GD9, and GD10 or GD12 (in 5 females) by gavage. Toxic manifestations were only seen in the high dose group, and included an increase in respiratory rate associated with cyanosis. No biologically significant decreases in body weight/weight gain or in food consumption were observed at the high dose following dose level reduction. Ten mg base/kg/day was therefore considered at or near the maternal NOEL. This observation is supported by the results of a previously conducted dose range-finding study (UIC/TRL Study No. 172) in which no effects were seen at 10 mg base/kg/day, whereas maternal mortality occurred at 20 mg base/kg/day. Females in the positive control group did not show any significant drug-related effects. At the 15/10 mg base/kg/day level, two litters were observed with fetuses having vertebral anomalies. No statistically significant increases in the number of litters with skeletal malformations resulted. However, since the malformations observed for the fetuses from both litters were of a similar nature, it is unclear if the vertebral anomalies were or were not a result of treatment with WR6026 Dihydrochloride at 15/10 mg base/kg/day (a maternally lethal dose level). Accordingly, 7 and possibly 15/10 mg base/kg/day was considered at or near the NOEL dose for developmental toxicity. In a previously conducted developmental toxicity study in rats, 2 mg base/kg/day was considered at or near the NOEL for fetal and maternal toxicity (UIC/TRL Study No. 171). Rats therefore demonstrated greater developmental sensitivity to WR6026 Dihydrochloride than rabbits. In the rat teratology study, WR6026 Dihydrochloride did not demonstrate a developmental hazard to rat fetuses except in maternally toxic doses (8 mg base/kg/day). At those dose levels, fetal body weights were reduced, but treatment-related malformations were not observed.</p>					

NE = No effect

RRJ = Respiratory rate increased

C = Cyanosis

(?) = Possible and/or transient effect

*mg/kg/day on GD9 & 10 (except for 5 females dosed on GD9 & 12)

FD = Found dead

MS = Moribund sacrifice

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Contract No.: DAMD17-92-C-2001
Task Order No.: UIC-13D
Study No.: 173

Table 2

DEVELOPMENTAL TOXICITY (SEGMENT II)
STUDY OF WR6026 DIHYDROCHLORIDE IN RABBITS

Dosage Formulation Analyses^a

Target Concentration (mg base/ml)	GD 4 ^b	% Target	Target Concentration (mg base/ml)	GD 21 ^c	% Target
0	0	-	0	0	-
3	2.944 ± 0.00	98.1	3	2.798 ± 0.15	93.3
7	6.958 ± 0.04	99.4	7	6.912 ± 0.36	98.7
15	15.248 ± 0.05	101.7	15	14.877 ± 0.04	99.2
10 ^d	10.273 ± 0.07	102.7	10	10.434 ± 0.67	104.3

^aMean ± standard deviation for triplicate runs.

^bGestation Day 4 (except for 10 mg base/ml which was analyzed when the high dose level was reduced; see footnote ^d)

^cGestation Day 21

^dThe high dose was reduced from 15 mg base/kg/day to 10 mg base/kg/day on gestation days 12-15
(the range of days reflects the study stagger-start over four days).

Table 3

DEVELOPMENTAL TOXICITY (SEGMENT II)
STUDY OF WR6026 DIHYDROCHLORIDE
IN RABBITS

DRAFT

SUMMARY OF CLINICAL SIGNS

STUDY: 173

SEX: FEMALE

	DOSE: (mg base/kg/day)	0	3	7	15/10 ^a	300 (mg/kg/day) ^b
GROUP:		1-F	2-F	3-F	4-F	5-F
Scheduled Sacrifice		20	20	19	16	20
Animal Found Dead		0	0	0	4	0
Sacrificed Moribund		0	0	1	0	0
Respiratory Rate Increased		0	0	0	14	0
Blue Sclera		0	0	0	3	0
Blue Ears		0	0	0	2	0
Total Number of Animals		20	20	20	20	20

^aThe high dose was reduced from 15 mg/kg/day to 10 mg/kg/day on GD12 - GD15 (the range of days reflects study stagger-start over 4 days)

^bRetinol palmitate given on GD9, and GD10 or GD12 (See Appendix 7; Study Deviations)

Table 4
DEVELOPMENTAL TOXICITY (SEGMENT II)
STUDY OF WR6026 DIHYDROCHLORIDE
IN RABBITS

DRAFT

SUMMARY OF BODY WEIGHTS (Kilograms)

STUDY: 173

SEX: FEMALE

PERIOD	DOSE: (mg base/kg/day)		3		7	15/10 ^a	300 (mg/kg/day) ^b
	GROUP:	0	1-F	2-F	3-F	4-F	5-F
DAY 0	MEAN		3.45	3.43	3.43	3.47	3.44
	S.D.		0.237	0.213	0.280	0.286	0.227
	N		20	20	20	20	20
DAY 5	MEAN		3.24	3.24	3.23	3.24	3.23
	S.D.		0.238	0.221	0.264	0.239	0.228
	N		20	20	20	20	20
DAY 6	MEAN		3.22	3.22	3.21	3.21	3.21
	S.D.		0.249	0.225	0.275	0.219	0.214
	N		20	20	20	20	20
DAY 7	MEAN		3.27	3.24	3.23	3.21	3.23
	S.D.		0.253	0.211	0.237	0.218	0.219
	N		20	20	20	20	20
DAY 8	MEAN		3.28	3.28	3.25	3.19	3.25
	S.D.		0.237	0.231	0.263	0.211	0.194
	N		20	20	20	20	20
DAY 9	MEAN		3.28	3.30	3.23	3.22	3.27
	S.D.		0.243	0.226	0.227	0.190	0.211
	N		20	20	20	20	20
DAY 10	MEAN		3.30	3.31	3.25	3.21	3.26
	S.D.		0.239	0.216	0.229	0.187	0.201
	N		20	20	20	19	20
DAY 11	MEAN		3.31	3.32	3.28	3.21	3.27
	S.D.		0.216	0.202	0.242	0.207	0.201
	N		20	20	20	18	20
DAY 12	MEAN		3.34	3.36	3.29	3.17	3.29
	S.D.		0.220	0.216	0.249	0.228	0.224
	N		20	20	20	18	20
DAY 13	MEAN		3.38	3.37	3.31	3.17	3.32
	S.D.		0.253	0.215	0.243	0.239	0.211
	N		20	20	20	18	20

Analysis of Variance using DUNNETT'S Procedure

^aThe high dose was reduced from 15 mg/kg/day to 10 mg/kg/day on GD12 - GD15 (the range of days reflects study stagger-start over 4 days)

^bRetinol palmitate given on GD9, and GD10 or GD12 (See Appendix 7; Study Deviations)

Table 4 (contd.)
DEVELOPMENTAL TOXICITY (SEGMENT II)
STUDY OF WR6026 DIHYDROCHLORIDE
IN RABBITS

DRAFT

SUMMARY OF BODY WEIGHTS (Kilograms)

STUDY: 173

SEX: FEMALE

PERIOD	DOSE: (mg base/kg/day)	0	3	7	15/10 ^a	300 (mg/kg/day) ^b
	GROUP:	1-F	2-F	3-F	4-F	5-F
DAY 14	MEAN	3.40	3.41	3.35	3.17*	3.35
	S.D.	0.225	0.220	0.280	0.285	0.208
	N	20	20	20	17	20
DAY 15	MEAN	3.46	3.45	3.37	3.24	3.40
	S.D.	0.241	0.219	0.258	0.264	0.207
	N	20	20	19	16	20
DAY 16	MEAN	3.46	3.45	3.41	3.27	3.41
	S.D.	0.226	0.207	0.267	0.261	0.223
	N	20	20	19	16	20
DAY 17	MEAN	3.48	3.46	3.42	3.29	3.42
	S.D.	0.220	0.208	0.254	0.267	0.230
	N	20	20	19	16	20
DAY 18	MEAN	3.46	3.45	3.42	3.30	3.40
	S.D.	0.228	0.208	0.241	0.275	0.236
	N	20	20	19	16	20
DAY 24	MEAN	3.54	3.54	3.52	3.40	3.42
	S.D.	0.229	0.198	0.270	0.279	0.232
	N	20	20	19	16	20
DAY 29	MEAN	3.61	3.61	3.54	3.45	3.50
	S.D.	0.210	0.206	0.290	0.282	0.262
	N	20	20	19	16	20

* P less than .05

Analysis of Variance using DUNNETT'S Procedure

^aThe high dose was reduced from 15 mg/kg/day to 10 mg/kg/day on GD12 - GD15 (the range of days reflects study stagger-start over 4 days)

^bRetinol palmitate given on GD9, and GD10 or GD12 (See Appendix 7; Study Deviations)

Table 5
DEVELOPMENTAL TOXICITY (SEGMENT II)
STUDY OF WR6026 DIHYDROCHLORIDE
IN RABBITS

DRAFT

SUMMARY OF WEIGHT GAINS (Kilograms)

STUDY: 173

SEX: FEMALE

PERIOD ^a	DOSE: (mg base/kg/day) GROUP:	0	3	7	15/10 ^c	300 (mg/kg/day) ^d
		1-F	2-F	3-F	4-F	5-F
DAY 7 ^b	MEAN	0.05	0.02	0.02	0.01	0.03
	S.D.	0.062	0.048	0.076	0.052	0.063
	N	20	20	20	20	20
DAY 8	MEAN	0.01	0.04	0.02	-0.03	0.02
	S.D.	0.051	0.057	0.046	0.048	0.052
	N	20	20	20	20	20
DAY 9	MEAN	-0.01	0.02	-0.02	0.03	0.03
	S.D.	0.056	0.039	0.076	0.059	0.038
	N	20	20	20	20	20
DAY 10	MEAN	0.03	0.01	0.02	0.00	-0.02
	S.D.	0.050	0.049	0.062	0.046	0.057
	N	20	20	20	19	20
DAY 11	MEAN	0.01	0.01	0.03	0.00	0.01
	S.D.	0.052	0.046	0.042	0.056	0.033
	N	20	20	20	18	20
DAY 12	MEAN	0.02	0.03	0.00	-0.04*	0.02
	S.D.	0.032	0.047	0.052	0.070	0.050
	N	20	20	20	18	20
DAY 13	MEAN	0.04	0.02	0.03	0.00	0.04
	S.D.	0.075	0.042	0.082	0.074	0.057
	N	20	20	20	18	20
DAY 14	MEAN	0.02	0.03	0.03	0.02	0.03
	S.D.	0.049	0.041	0.074	0.071	0.091
	N	20	20	20	17	20
DAY 15	MEAN	0.05	0.05	0.01	0.04	0.05
	S.D.	0.036	0.053	0.059	0.037	0.098
	N	20	20	19	16	20
DAY 16	MEAN	0.00	0.00	0.03	0.03	0.01
	S.D.	0.058	0.056	0.060	0.040	0.044
	N	20	20	19	16	20

* P less than .05

Analysis of Variance using DUNNETT'S Procedure

^a Successive periods

^b Baseline is day 6

^c The high dose was reduced from 15 mg/kg/day to 10 mg/kg/day on G012 - G015 (the range of days reflects study stagger-start over 4 days)

^d Retinol palmitate given on G09, and G010 or G012 (See Appendix 7; Study Deviations)

Table 5 (contd.)
DEVELOPMENTAL TOXICITY (SEGMENT II)
STUDY OF WR6026 DIHYDROCHLORIDE
IN RABBITS

SUMMARY OF WEIGHT GAINS (Kilograms)

STUDY: 173

SEX: FEMALE

PERIOD ^a		DOSE: (mg base/kg/day)				
		0	3	7	15/10 ^b	300 (mg/kg/day) ^c
	GROUP:	1-F	2-F	3-F	4-F	5-F
DAY 17	MEAN	0.02	0.01	0.01	0.02	0.00
	S.D.	0.045	0.063	0.069	0.030	0.048
	N	20	20	19	16	20
DAY 18	MEAN	-0.02	-0.01	0.00	0.01	-0.02
	S.D.	0.060	0.056	0.043	0.037	0.045
	N	20	20	19	16	20
DAY 24	MEAN	0.08	0.09	0.11	0.10	0.03*
	S.D.	0.051	0.054	0.067	0.077	0.057
	N	20	20	19	16	20
DAY 29	MEAN	0.07	0.07	0.02	0.06	0.08
	S.D.	0.063	0.048	0.141	0.056	0.084
	N	20	20	19	16	20
TOTAL GAIN	MEAN	0.38	0.39	0.36	0.31	0.30
	S.D.	0.111	0.110	0.225	0.163	0.134
	N	20	20	19	16	20

* P less than .05

Analysis of Variance using DUNNETT'S Procedure

^a Successive periods^b The high dose was reduced from 15 mg/kg/day to 10 mg/kg/day on GD12 - GD15 (the range of days reflects study stagger-start over 4 days)^c Retinol palmitate given on GD9, and GD10 or GD12 (See Appendix 7; Study Deviations)

Table 6

DEVELOPMENTAL TOXICITY (SEGMENT II)
STUDY OF WR6026 DIHYDROCHLORIDE
IN RABBITS

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SUMMARY OF DAILY MEAN FOOD CONSUMPTION (Grams)

STUDY: 173

SEX: FEMALE

PERIOD	DOSE: (mg base/kg/day) GROUP:	0 1-F	3 2-F	7 3-F	15/10 ^a 4-F	300 (mg/kg/day) ^b 5-F
DAY 8	INTAKE (g)	130	130	124	124	130
	S.D.	0.0	0.0	29.1	18.8	0.0
	N	20	20	20	20	20
DAY 10	INTAKE (g)	130	130	122	123	130
	S.D.	0.0	0.0	27.5	26.8	0.0
	N	20	20	20	19	20
DAY 12	INTAKE (g)	130	130	122	94 *	130
	S.D.	0.0	0.0	21.9	49.5	0.0
	N	20	20	20	18	20
DAY 15	INTAKE (g)	130	130	129	119 *	130
	S.D.	0.0	0.0	5.0	30.0	0.0
	N	20	20	19	16	20
DAY 18	INTAKE (g)	129	130	130	130	130
	S.D.	4.5	0.0	0.0	0.0	0.0
	N	20	20	19	16	20
DAY 24	INTAKE (g)	130	130	130	130	130
	S.D.	0.0	0.0	0.0	0.0	0.0
	N	20	20	19	16	20
DAY 29	INTAKE (g)	130	130	125	130	130
	S.D.	0.0	0.0	14.5	0.0	0.0
	N	20	20	19	16	20

* P less than .05

Statistical Analysis by Kruskal-Wallis test and Mann-Whitney U test

^aThe high dose was reduced from 15 mg/kg/day to 10 mg/kg/day on GD12 - GD15 (the range of days reflects study stagger-start over 4 days)

^bRetinol palmitate given on GD9, and GD10 or GD12 (See Appendix 7; Study Deviations)

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Table 7

DEVELOPMENTAL TOXICITY (SEGMENT II)
STUDY OF WR6026 DIHYDROCHLORIDE IN RABBITS

Summary of Cesarean-Section Data and Fetal Evaluations

	WR6026 Dihydrochloride					Retinol Palmitate
	0	3	7	15/10 ^a	300 mg/kg/day ^b	
Dose Level (mg base/kg/day)	0	3	7	15/10 ^a	300 mg/kg/day ^b	
Pregnant/On Study	20/20	18/20	20/20	20/20	19/20	
Early Pregnancy Termination/Term Litters	0/20	0/18	1/19	4/16	0/19	
Uterine Weight (g)	365.22 ± 78.74	399.64 ± 121.10	394.36 ± 86.08	384.00 ± 118.11	294.20 ± 174.71	
Early Resorptions (No.)	0.6 ± 1.1	0.4 ± 0.7	0.2 ± 0.5	0.9 ± 1.7	2.9 ± 2.3 ^c	
Viable Fetuses (No.)	6.9 ± 1.7	8.1 ± 2.7 ^c	7.8 ± 1.7	7.3 ± 2.5	5.2 ± 3.5	
Post-implantation loss (%)	8.8 ± 13.3	4.7 ± 6.6	5.2 ± 8.8	12.3 ± 22.7	40.7 ^c ± 36.3	
Total Implantation Loss (%)	16.1 ± 16.8	13.7 ± 23.4	10.8 ± 10.1	15.4 ± 19.7	44.3 ^c ± 37.3	
Fetal Body Weight (g) ^d - Males	38.28 ± 4.92	36.97 ± 5.08	35.76 ± 5.19	37.27 ± 5.18	39.51 ± 5.33	
- Females	38.93 ± 5.58	36.42 ± 6.22	35.44 ± 4.82	37.14 ± 4.06	38.66 ± 4.40	
Litters with External Malformations (%)	1(5)	1(5.6)	1(5.3)	1(6.3)	15(93.8) ^e	
Litters with Skeletal Malformations (%)	2(10)	2(11.1)	2(10.5)	4(25)	16(100) ^e	
Litters with Visceral Malformations (%)	1(5)	1(5.6)	0(0)	1(6.3)	10(62.5) ^e	

^aThe high dose was reduced to 10 mg base/kg/day on gestation days 12-15 (the range of days reflects study stagger-start over four days)

^bmg/kg/day on GD9 and GD10 (except for 5 females were dosed on GD9 & 12)

^cStatistically significant from vehicle control group using Kruskal-Wallis/Mann-Whitney U test (p ≤ 0.05)

^dData indicate mean of the total of the litter means

^eStatistically significant from vehicle control group using the Fisher's Exact test (p ≤ 0.05)

Summarized data are presented as Mean ± SD

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APPENDIX 1

Analytical Chemistry Report

DEVELOPMENTAL TOXICITY (SEGMENT II) STUDY OF
WR6026 DIHYDROCHLORIDE IN RABBITS

UIC/TRL STUDY NUMBER 173

Part I: Identity, Purity, and Stability Study of WR6026

Part II: Dosing Solutions Analysis of WR6026 in Aqueous Solution

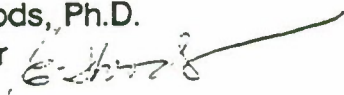
Analysts: Thomas Tolhurst
A. Karl Larsen, Jr.

Study Site: Drug Disposition Research Laboratory
College of Pharmacy
University of Illinois at Chicago
Chicago, Illinois 60612

Sponsor: Toxicology Research Laboratory
University of Illinois at Chicago
Chicago, Illinois 60612

Report Prepared by: Thomas Tolhurst

Report Prepared: March 29, 1995

Approved: March 29, 1995
Dr. Euguen F. Woods, Ph.D.
Laboratory Director 

Part I: Identity, Purity and Stability Study of WR6026**Objective**

The objective of this study was to confirm the identity and establish the purity and stability of WR6026.

Identification**GC-MS System**

Gas Chromatograph: Hewlett-Packard Series II

Mass Selective Detector: Hewlett-Packard Model 5970

Analytical Column: 30 m x 0.25 mm ID, DB-5 with a 3 micron film thickness.

GC Parameters: Injector temp. 250°C, oven temp. 70°C initial, 280°C final, 15°C/minute ramp, carrier gas - helium, flow rate 2ml/minute, split ratio 10:1

Procedure

The subject sample (WR6026 dihydrochloride) was submitted by the Toxicology Research Laboratory. The sample was dissolved in hexane:ethanol (1:1) to a concentration of 1 µg base/ml and a 2 µl aliquot was injected on the column. The MSD scanned from 40 amu to 400 amu at a rate of 1 scan per second.

Results - GC-MS

The mass spectrum indicates a molecular ion m/e of 343 which is in agreement with the WR6026 free base molecular weight. Major fragments of the WR6026 sample are m/e 269, 201, and 86, which correspond to the finding observed by SRI International (see Report No. 394, August 6, 1981).

Figure 1 shows the mass spectrum of the WR6026 sample.

Purity**Experimental**

The subject sample (WR6026 dihydrochloride) was supplied by the Toxicology Research Laboratory and stored at -20°C when it was not analyzed.

Description

A fine yellow powder, no obvious odor.

Spectrum

An ultraviolet spectrum (Figure 2) recorded on a Spectra Physics multiwavelength detector interfaced with an IBM Personal Data System 2 was obtained from a 1.5 mg/ml solution of WR6026 prepared in mobile phase. Maximal absorptivity was observed at 264 nm.

HPLC System

Solvent Delivery System:	Waters 600E Multisolvent Delivery System
Injector:	Rheodyne 7125 with 20 μ l sample loop
Analytical Column:	Phenomenex C ₁₈ , 10 μ , 300 x 3.9 mm
Detector:	Waters 484 Tunable Absorbance Detector, 0.05 AUFS, 264 nm
Integrator:	Waters 746 Data Module
Mobile Phase:	9.0 ml α -phosphoric acid and 6.8 g sodium acetate per liter of methanol:water (60:40, v/v), flow 1.0 ml/minute

Procedure

Five solutions of WR6026 were prepared as follows. Twenty mg of a WR6026 dihydrochloride sample was weighed into a 50 ml polypropylene volumetric flask. The sample was dissolved in and the volume brought to mark with mobile phase. A 20 μ l aliquot of each solution was immediately chromatographed at 264 nm. The procedure was conducted on two subject samples, one submitted prior to and the other following completion of Study No. 173.

Calculation of Results

Quantitations were based on the assumption of equal detector response per unit weight of all UV-absorbing components.

Areas of WR6026 and other detectable components in the subject sample chromatograms were employed in the following equation to calculate the percentage of WR6026 present in the sample:

$$\% \text{PURITY} = (\text{area of WR6026} / \text{total area}) \times 100$$

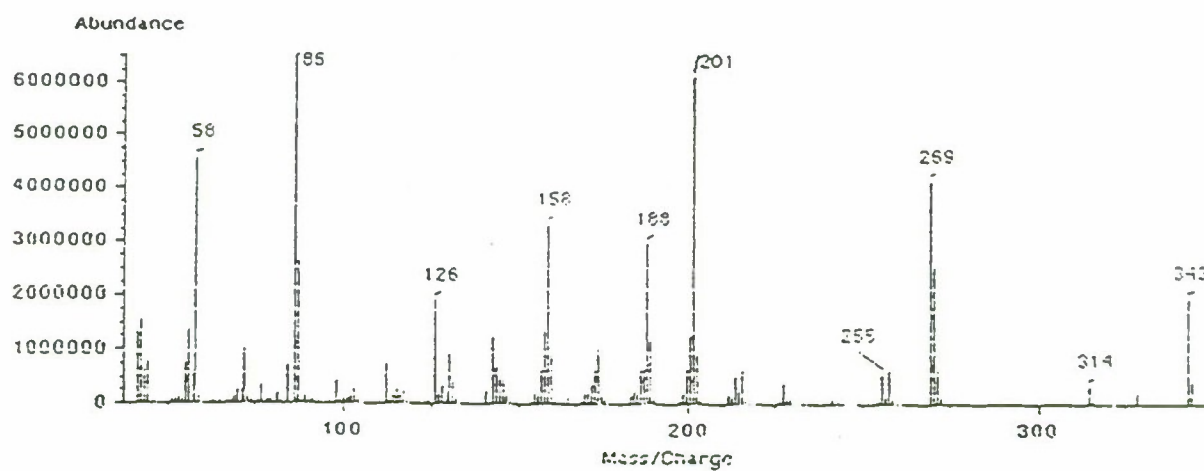
Results

Typical chromatograms are shown in Figure 3. The subject samples were found to contain less than 1% of UV-absorbing impurities (264 nm). Percent purity of the initial WR6026 sample was found to be 99.583, standard deviation ± 0.051 ; the terminal sample purity 99.492 ± 0.058 . The assay results are presented in Tables 1 and 2.

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FIGURE 1

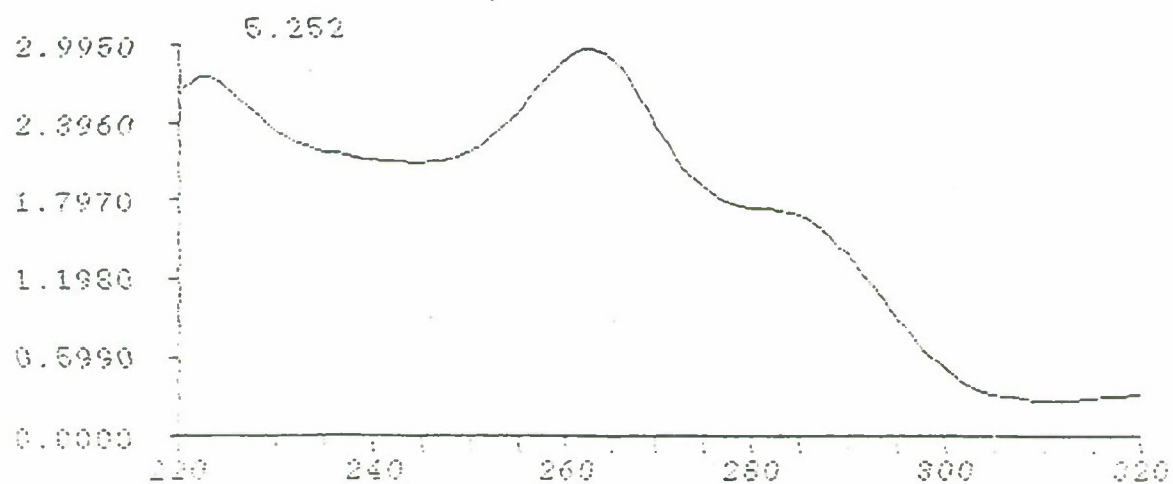
MASS SPECTRUM OF WR6026 SAMPLE



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FIGURE 2

ULTRAVIOLET SPECTRUM OF WR6026



Spectra Display: \FOCUS\WR6026_4.BPF

FIGURE 3

CHROMATOGRAMS OF WR6026 SAMPLE, 264 NM,
A - INITIAL SAMPLE, B - TERMINAL SAMPLE

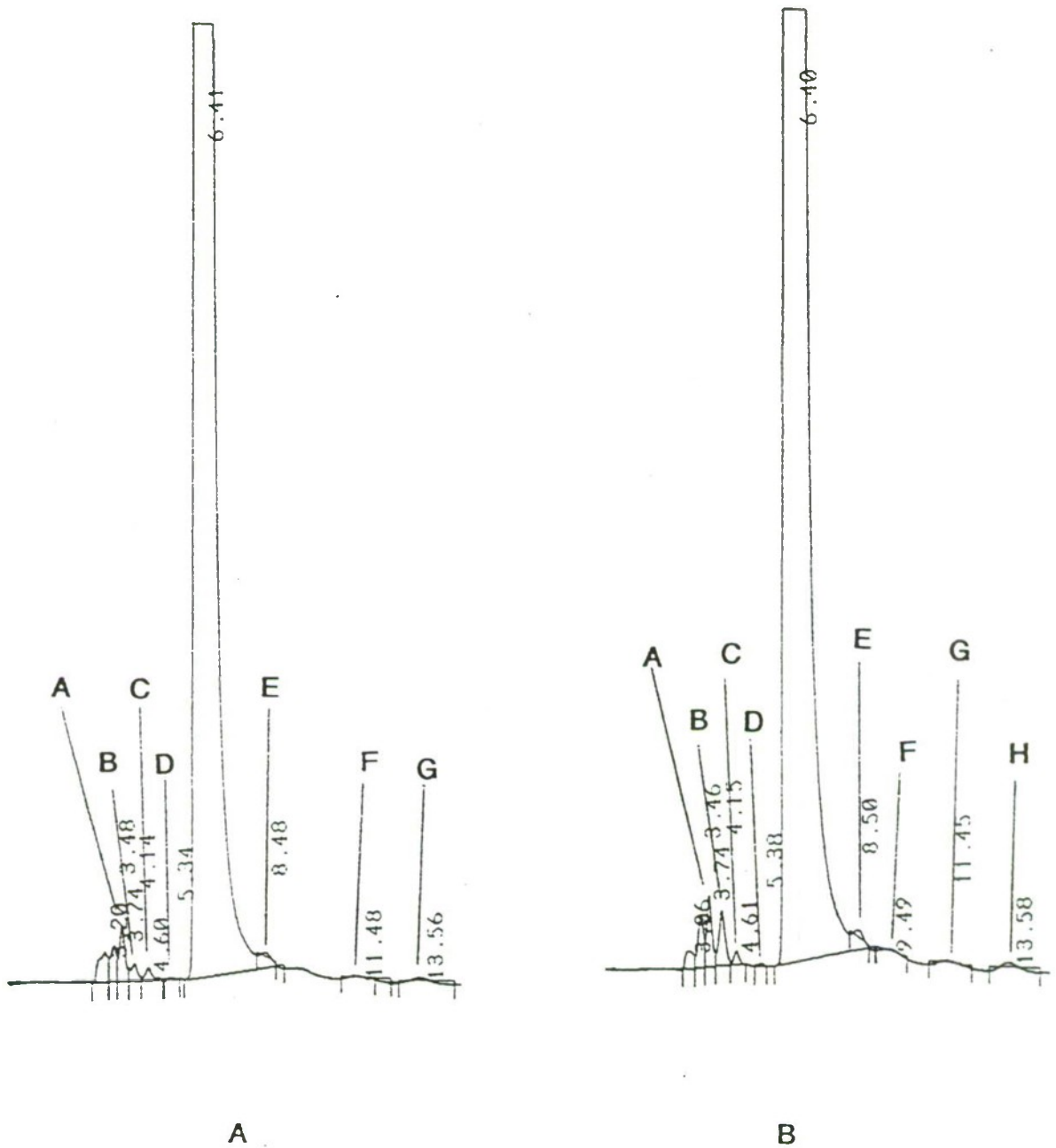


Table 1

Purity Data for WR6026
Initial Sample

Solutions

Peak Identity	1	2	3	4	5
A	39319	40252	48751	55780	46767
B	10386	14884	16610	34226	30774
C	8202	10980	10413	11440	12486
D	1281	1373	2237	1980	2339
WR6026	22520474	22758063	25808038	35280468	29972036
E	9732	8987	11733	14546	9899
F	¹ -	¹ -	5790	17794	15223
G	11409	14716	17076	21596	19751
%Purity	99.645	99.601	99.607	99.519	99.544

¹ - peak not integrated

Mean \pm S.D. - 99.583 \pm 0.051

Table 2

Purity Data for WR6026
Terminal Sample

Solutions

Peak Identity	1	2	3	4	5
A	37230	47375	46911	49003	49110
B	30245	41626	45358	50948	58761
C	7207	11257	9812	16203	10374
D	2469	2229	1765	¹ -	2490
WR6026	31771946	31131360	32920235	32811010	33438184
E	12623	11281	12697	13904	12038
F	11225	13518	11006	13545	17044
G	9567	16813	15435	17861	15456
H	20570	19987	21151	19734	20707
% Purity	99.589	99.476	99.496	99.451	99.447

¹ - peak not integrated

Mean \pm S.D. - 99.492 \pm 0.058

Part II: Dosing Formulations Analysis of WR6026 in Aqueous Solution**Introduction**

Samples from Study No. 173 were submitted by the Toxicology Research Laboratory to the Drug Disposition Research Laboratory for the quantitation of WR6026 in dosing formulations. Samples were received on March 10, March 21 and March 27, 1995. All samples submitted were analyzed by high performance liquid chromatography by a previously described analytical method (see UIC/TRL Study No. 091 analytical chemistry report dated April 2, 1993, Part I). The molar fraction coefficient is 0.825.

Results

Results of dosing solutions for Study No. 173 are found in Table 3. All dosing solutions analyzed were within 10% of their target values.

Table 3

Results of Dosing Solutions
for Study No. 173

March 10, 1995

Sample Identification	Target Concentrations (mg base/ml)	Mean Concentrations \pm S.D. (mg base/ml)
WHITE	0	0
YELLOW	3	2.944 ± 0.004
BLUE	7	6.958 ± 0.042
BLACK	15	15.248 ± 0.049

March 21, 1995

Sample Identification	Target Concentrations (mg base/ml)	Mean Concentrations \pm S.D. (mg base/ml)
ORANGE	10	10.273 ± 0.066

March 27, 1995

Sample Identification	Target Concentrations (mg base/ml)	Mean Concentrations \pm S.D. (mg base/ml)
WHITE	0	0
YELLOW	3	2.798 ± 0.150
BLUE	7	6.912 ± 0.362
BLACK	15	14.877 ± 0.037
ORANGE	10	10.434 ± 0.669

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APPENDIX 2

Individual Maternal Clinical Signs

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DEVELOPMENTAL TOXICITY (SEGMENT II)
STUDY OF WR6026 DIHYDROCHLORIDE
IN RABBITS

INDIVIDUAL CLINICAL SIGNS

STUDY: 173
DAY 6-DAY 29GROUP: 1-F
DOSE: 0 (mg base/kg/day)

SEX: FEMALE

ANIMAL #	OBSERVATIONS	SEVERITY	LOC	TIME OCCURRED
701	Normal Scheduled Sacrifice			DAY 6-DAY 28 DAY 29
702	Normal Scheduled Sacrifice			DAY 6-DAY 28 DAY 29
703	Normal Scheduled Sacrifice			DAY 6-DAY 28 DAY 29
704	Normal Scheduled Sacrifice			DAY 6-DAY 28 DAY 29
705	Normal Scheduled Sacrifice			DAY 6-DAY 28 DAY 29
706	Normal Scheduled Sacrifice			DAY 6-DAY 28 DAY 29
707	Normal Scheduled Sacrifice			DAY 6-DAY 28 DAY 29
708	Normal Scheduled Sacrifice			DAY 6-DAY 28 DAY 29
709	Normal Scheduled Sacrifice			DAY 6-DAY 28 DAY 29
710	Normal Scheduled Sacrifice			DAY 6-DAY 28 DAY 29
711	Normal Scheduled Sacrifice			DAY 6-DAY 28 DAY 29
712	Normal Scheduled Sacrifice			DAY 6-DAY 28 DAY 29
713	Normal Scheduled Sacrifice			DAY 6-DAY 28 DAY 29

DEVELOPMENTAL TOXICITY (SEGMENT II)
STUDY OF WR6026 DIHYDROCHLORIDE
IN RABBITS

INDIVIDUAL CLINICAL SIGNS

STUDY: 173
DAY 6-DAY 29GROUP: 1-F
DOSE: 0 (mg base/kg/day)

SEX: FEMALE

ANIMAL #	OBSERVATIONS	SEVERITY	LOC	TIME OCCURRED
714	Normal Scheduled Sacrifice			DAY 6-DAY 28 DAY 29
715	Normal Scheduled Sacrifice			DAY 6-DAY 28 DAY 29
716	Normal Scheduled Sacrifice			DAY 6-DAY 28 DAY 29
717	Normal Scheduled Sacrifice			DAY 6-DAY 28 DAY 29
718	Normal Scheduled Sacrifice			DAY 6-DAY 28 DAY 29
719	Normal Scheduled Sacrifice			DAY 6-DAY 28 DAY 29
720	Normal Scheduled Sacrifice			DAY 6-DAY 28 DAY 29

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DEVELOPMENTAL TOXICITY (SEGMENT II)
STUDY OF WR6026 DIHYDROCHLORIDE
IN RABBITS

INDIVIDUAL CLINICAL SIGNS

STUDY: 173
DAY 6-DAY 29GROUP: 2-F
DOSE: 3 (mg base/kg/day)

SEX: FEMALE

ANIMAL #	OBSERVATIONS	SEVERITY	LOC	TIME OCCURRED
721	Normal Scheduled Sacrifice			DAY 6-DAY 28 DAY 29
722	Normal Scheduled Sacrifice			DAY 6-DAY 28 DAY 29
723	Normal Scheduled Sacrifice			DAY 6-DAY 28 DAY 29
724	Normal Scheduled Sacrifice			DAY 6-DAY 28 DAY 29
725	Normal Scheduled Sacrifice			DAY 6-DAY 28 DAY 29
726	Normal Scheduled Sacrifice			DAY 6-DAY 28 DAY 29
727	Normal Scheduled Sacrifice			DAY 6-DAY 28 DAY 29
728	Normal Scheduled Sacrifice			DAY 6-DAY 28 DAY 29
729	Normal Scheduled Sacrifice			DAY 6-DAY 28 DAY 29
730	Normal Scheduled Sacrifice			DAY 6-DAY 28 DAY 29
731	Normal Scheduled Sacrifice			DAY 6-DAY 28 DAY 29
732	Normal Scheduled Sacrifice			DAY 6-DAY 28 DAY 29
733	Normal Scheduled Sacrifice			DAY 6-DAY 28 DAY 29

DEVELOPMENTAL TOXICITY (SEGMENT II)
STUDY OF WR6026 DIHYDROCHLORIDE
IN RABBITS

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INDIVIDUAL CLINICAL SIGNS

STUDY: 173
DAY 6-DAY 29

GROUP: 2-F
DOSE: 3 (mg base/kg/day)

SEX: FEMALE

ANIMAL #	OBSERVATIONS	SEVERITY	LOC	TIME OCCURRED
734	Normal Scheduled Sacrifice			DAY 6-DAY 28 DAY 29
735	Normal Scheduled Sacrifice			DAY 6-DAY 28 DAY 29
736	Normal Scheduled Sacrifice			DAY 6-DAY 28 DAY 29
737	Normal Scheduled Sacrifice			DAY 6-DAY 28 DAY 29
738	Normal Scheduled Sacrifice			DAY 6-DAY 28 DAY 29
739	Normal Scheduled Sacrifice			DAY 6-DAY 28 DAY 29
740	Normal Scheduled Sacrifice			DAY 6-DAY 28 DAY 29

DEVELOPMENTAL TOXICITY (SEGMENT II)
STUDY OF WR6026 DIHYDROCHLORIDE
IN RABBITS

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INDIVIDUAL CLINICAL SIGNS

STUDY: 173
DAY 6-DAY 29

GROUP: 3-F
DOSE: 7 (mg base/kg/day)

SEX: FEMALE

ANIMAL #	OBSERVATIONS	SEVERITY	LOC	TIME OCCURRED
741	Normal Scheduled Sacrifice			DAY 6-DAY 28 DAY 29
742	Normal Scheduled Sacrifice			DAY 6-DAY 28 DAY 29
743	Normal Scheduled Sacrifice			DAY 6-DAY 28 DAY 29
744	Normal Scheduled Sacrifice			DAY 6-DAY 28 DAY 29
745	Normal Scheduled Sacrifice			DAY 6-DAY 28 DAY 29
746	Normal Scheduled Sacrifice			DAY 6-DAY 28 DAY 29
747	Normal Scheduled Sacrifice			DAY 6-DAY 28 DAY 29
748	Normal Scheduled Sacrifice			DAY 6-DAY 28 DAY 29
749	Normal Scheduled Sacrifice			DAY 6-DAY 28 DAY 29
750	Normal Scheduled Sacrifice			DAY 6-DAY 28 DAY 29
751	Normal Scheduled Sacrifice			DAY 6-DAY 28 DAY 29
752	Normal Scheduled Sacrifice			DAY 6-DAY 28 DAY 29
753	Normal Scheduled Sacrifice			DAY 6-DAY 28 DAY 29

DEVELOPMENTAL TOXICITY (SEGMENT II)
STUDY OF WR6026 DIHYDROCHLORIDE
IN RABBITS

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INDIVIDUAL CLINICAL SIGNS

STUDY: 173
DAY 6-DAY 29

GROUP: 3-F
DOSE: 7 (mg base/kg/day)

SEX: FEMALE

ANIMAL #	OBSERVATIONS	SEVERITY	LOC	TIME OCCURRED
754	Normal Scheduled Sacrifice			DAY 6-DAY 28 DAY 29
755	Normal Scheduled Sacrifice			DAY 6-DAY 28 DAY 29
756	Normal Sacrificed Moribund			DAY 6-DAY 15 DAY 14
757	Normal Scheduled Sacrifice			DAY 6-DAY 28 DAY 29
758	Normal Scheduled Sacrifice			DAY 6-DAY 28 DAY 29
759	Normal Scheduled Sacrifice			DAY 6-DAY 28 DAY 29
760	Normal Scheduled Sacrifice			DAY 6-DAY 28 DAY 29

DEVELOPMENTAL TOXICITY (SEGMENT II)
STUDY OF WR6026 DIHYDROCHLORIDE
IN RABBITS

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INDIVIDUAL CLINICAL SIGNS

STUDY: 173
DAY 6-DAY 29

GROUP: 4-F
DOSE: 15/10 (mg base/kg/day)^a

SEX: FEMALE

ANIMAL #	OBSERVATIONS	SEVERITY	LOC	TIME OCCURRED
761	Normal Normal Respiratory Rate Increased Scheduled Sacrifice			DAY 6-DAY 14 DAY 17-DAY 28 DAY 15-DAY 16 DAY 29
762	Normal Normal Respiratory Rate Increased Scheduled Sacrifice			DAY 6-DAY 14 DAY 17-DAY 28 DAY 15-DAY 16 DAY 29
763	Animal Found Dead Normal Respiratory Rate Increased			DAY 14 DAY 6-DAY 12 DAY 13
764	Blue Sclera Blue Ears Animal Found Dead Normal Respiratory Rate Increased			DAY 12-DAY 14 DAY 13-DAY 14 DAY 15 DAY 6-DAY 10 DAY 11-DAY 14
765	Animal Found Dead Normal			DAY 10 DAY 6-DAY 9
766	Normal Normal Normal Respiratory Rate Increased Respiratory Rate Increased Scheduled Sacrifice			DAY 6-DAY 12 DAY 15 DAY 18-DAY 28 DAY 13-DAY 14 DAY 16-DAY 17 DAY 29
767	Normal Normal Respiratory Rate Increased Scheduled Sacrifice			DAY 6-DAY 12 DAY 14-DAY 28 DAY 13 DAY 29
768	Normal Scheduled Sacrifice			DAY 6-DAY 28 DAY 29

^aThe high dose was reduced from 15 mg/kg/day to 10 mg/kg/day on GD12 - GD15 (the range of days reflects study stagger-start over 4 days)

DEVELOPMENTAL TOXICITY (SEGMENT II)
STUDY OF WR6026 DIHYDROCHLORIDE
IN RABBITS

INDIVIDUAL CLINICAL SIGNS

STUDY: 173
DAY 6-DAY 29

GROUP: 4-F
DOSE: 15/10 (mg base/kg/day)^a

SEX: FEMALE

ANIMAL #	OBSERVATIONS	SEVERITY	LOC	TIME OCCURRED
769	Normal			DAY 6-DAY 12
	Normal			DAY 17
	Normal			DAY 19-DAY 28
	Respiratory Rate Increased			DAY 13-DAY 16
	Respiratory Rate Increased			DAY 18
	Scheduled Sacrifice			DAY 29
770	Normal			DAY 6-DAY 28
	Scheduled Sacrifice			DAY 29
771	Normal			DAY 6-DAY 11
	Normal			DAY 14-DAY 28
	Respiratory Rate Increased			DAY 12-DAY 13
	Scheduled Sacrifice			DAY 29
772	Normal			DAY 6-DAY 12
	Normal			DAY 14-DAY 28
	Respiratory Rate Increased			DAY 13
	Scheduled Sacrifice			DAY 29
773	Normal			DAY 6-DAY 11
	Normal			DAY 23-DAY 28
	Respiratory Rate Increased			DAY 12-DAY 22
	Scheduled Sacrifice			DAY 29
774	Normal			DAY 6-DAY 28
	Scheduled Sacrifice			DAY 29
775	Animal Found Dead			DAY 11
	Normal			DAY 6-DAY 9
	Respiratory Rate Increased			DAY 10
776	Blue Sclera			DAY 13
	Blue Sclera			DAY 15
	Blue Ears			DAY 13
	Normal			DAY 6-DAY 10
	Normal			DAY 19-DAY 28
	Respiratory Rate Increased			DAY 11-DAY 18
	Scheduled Sacrifice			DAY 29

^aThe high dose was reduced from 15 mg/kg/day to 10 mg/kg/day on GD12 - GD15 (the range of days reflects study stagger-start over 4 days)

DEVELOPMENTAL TOXICITY (SEGMENT II)
STUDY OF WR6026 DIHYDROCHLORIDE
IN RABBITS

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INDIVIDUAL CLINICAL SIGNS

STUDY: 173
DAY 6-DAY 29

GROUP: 4-F
DOSE: 15/10 (mg base/kg/day)^a

SEX: FEMALE

ANIMAL #	OBSERVATIONS	SEVERITY	LOC	TIME OCCURRED
777	Blue Sclera			DAY 12-DAY 15
	Blue Sclera			DAY 17-DAY 18
	Normal			DAY 6-DAY 10
	Normal			DAY 19-DAY 28
	Respiratory Rate Increased			DAY 11-DAY 18
	Scheduled Sacrifice			DAY 29
778	Normal			DAY 6-DAY 28
	Scheduled Sacrifice			DAY 29
779	Normal			DAY 6-DAY 28
	Scheduled Sacrifice			DAY 29
780	Normal			DAY 6-DAY 10
	Normal			DAY 15-DAY 28
	Respiratory Rate Increased			DAY 11-DAY 14
	Scheduled Sacrifice			DAY 29

^aThe high dose was reduced from 15 mg/kg/day to 10 mg/kg/day on GD12 - GD15 (the range of days reflects study stagger-start over 4 days)

DEVELOPMENTAL TOXICITY (SEGMENT II)
STUDY OF WR6026 DIHYDROCHLORIDE
IN RABBITS

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INDIVIDUAL CLINICAL SIGNS

STUDY: 173
DAY 6-DAY 29

GROUP: 5-F
DOSE: 300 (mg/kg/day)^a

SEX: FEMALE

ANIMAL #	OBSERVATIONS	SEVERITY	LOC	TIME OCCURRED
781	Normal Scheduled Sacrifice			DAY 9-DAY 28 DAY 29
782	Normal Scheduled Sacrifice			DAY 9-DAY 28 DAY 29
783	Normal Scheduled Sacrifice			DAY 9-DAY 28 DAY 29
784	Normal Scheduled Sacrifice			DAY 9-DAY 28 DAY 29
785	Normal Scheduled Sacrifice			DAY 9-DAY 28 DAY 29
786	Normal Scheduled Sacrifice			DAY 9-DAY 28 DAY 29
787	Normal Scheduled Sacrifice			DAY 9-DAY 28 DAY 29
788	Normal Scheduled Sacrifice			DAY 9-DAY 28 DAY 29
789	Normal Scheduled Sacrifice			DAY 9-DAY 28 DAY 29
790	Normal Scheduled Sacrifice			DAY 9-DAY 28 DAY 29
791	Normal Scheduled Sacrifice			DAY 9-DAY 28 DAY 29
792	Normal Scheduled Sacrifice			DAY 9-DAY 28 DAY 29
793	Normal Scheduled Sacrifice			DAY 9-DAY 28 DAY 29

^a Retinol palmitate given on GD9, and GD10 or GD12 (See Appendix 7; Study Deviations)

DEVELOPMENTAL TOXICITY (SEGMENT II)
STUDY OF WR6026 DIHYDROCHLORIDE
IN RABBITS

INDIVIDUAL CLINICAL SIGNS

STUDY: 173
DAY 6-DAY 29GROUP: 5-F
DOSE: 300 (mg/kg/day)^a

SEX: FEMALE

ANIMAL #	OBSERVATIONS	SEVERITY	LOC	TIME OCCURRED
794	Normal Scheduled Sacrifice			DAY 9-DAY 28 DAY 29
795	Normal Scheduled Sacrifice			DAY 9-DAY 28 DAY 29
796	Normal Scheduled Sacrifice			DAY 9-DAY 28 DAY 29
797	Normal Scheduled Sacrifice			DAY 9-DAY 28 DAY 29
798	Normal Scheduled Sacrifice			DAY 9-DAY 28 DAY 29
799	Normal Scheduled Sacrifice			DAY 9-DAY 28 DAY 29
800	Normal Scheduled Sacrifice			DAY 9-DAY 28 DAY 29

^a Retinol palmitate given on GD9, and GD10 or GD12 (See Appendix 7; Study Deviations)

DEVELOPMENTAL TOXICITY (SEGMENT II)
STUDY OF WR6026 DIHYDROCHLORIDE
IN RABBITS

INCIDENCE OF OBSERVATIONS

STUDY: 173

SEX: FEMALE

PERIOD	DOSE: (mg base/kg/day) GROUP:	0 1-F	3 2-F	7 3-F	15/10 ^a 4-F	300 (mg/kg/day) ^b 5-F
DAY 6						
No. Observed		20	20	20	20	0
Normal		20 100%	20 100%	20 100%	20 100%	0
DAY 7						
No. Observed		20	20	20	20	0
Normal		20 100%	20 100%	20 100%	20 100%	0
DAY 8						
No. Observed		20	20	20	20	0
Normal		20 100%	20 100%	20 100%	20 100%	0
DAY 9						
No. Observed		20	20	20	20	20
Normal		20 100%	20 100%	20 100%	20 100%	20 100%
DAY 10						
No. Observed		20	20	20	20	20
Animal Found Dead		0	0	0	1 5%	0
Normal		20 100%	20 100%	20 100%	18 90%	20 100%
Respiratory Rate Increased		0	0	0	1 5%	0
DAY 11						
No. Observed		20	20	20	19	20
Animal Found Dead		0	0	0	1 5%	0
Normal		20 100%	20 100%	20 100%	14 74%	20 100%
Respiratory Rate Increased		0	0	0	4 21%	0
DAY 12						
No. Observed		20	20	20	18	20
Normal		20 100%	20 100%	20 100%	12 67%	20 100%
Respiratory Rate Increased		0	0	0	6 33%	0
Blue Sclera		0	0	0	2 11%	0
DAY 13						
No. Observed		20	20	20	18	20
Normal		20 100%	20 100%	20 100%	7 39%	20 100%
Respiratory Rate Increased		0	0	0	11 61%	0
Blue Sclera		0	0	0	3 17%	0
Blue Ears		0	0	0	2 11%	0

^aThe high dose was reduced from 15 mg/kg/day to 10 mg/kg/day on GD12 - GD15 (the range of days reflects study stagger-start over 4 days)

^bRetinol palmitate given on GD9, and GD10 or GD12 (See Appendix 7; Study Deviations)

DEVELOPMENTAL TOXICITY (SEGMENT II)
STUDY OF WR6026 DIHYDROCHLORIDE
IN RABBITS

INCIDENCE OF OBSERVATIONS

STUDY: 173

SEX: FEMALE

PERIOD	DOSE: (mg base/kg/day) GROUP:	0 1-F	3 2-F	7 3-F	15/10 ^a 4-F	300 (mg/kg/day) ^b 5-F
DAY 14						
No. Observed		20	20	20	18	20
Animal Found Dead		0	0	0	1 6%	0
Sacrificed Moribund		0	0	1 5%	0	0
Normal		20 100%	20 100%	20 100%	10 56%	20 100%
Respiratory Rate Increased		0	0	0	7 39%	0
Blue Sclera		0	0	0	2 11%	0
Blue Ears		0	0	0	1 6%	0
DAY 15						
No. Observed		20	20	19	17	20
Animal Found Dead		0	0	0	1 6%	0
Normal		20 100%	20 100%	19 100%	10 59%	20 100%
Respiratory Rate Increased		0	0	0	6 35%	0
Blue Sclera		0	0	0	2 12%	0
DAY 16						
No. Observed		20	20	19	16	20
Normal		20 100%	20 100%	19 100%	9 56%	20 100%
Respiratory Rate Increased		0	0	0	7 44%	0
DAY 17						
No. Observed		20	20	19	16	20
Normal		20 100%	20 100%	19 100%	12 75%	20 100%
Respiratory Rate Increased		0	0	0	4 25%	0
Blue Sclera		0	0	0	1 6%	0
DAY 18						
No. Observed		20	20	19	16	20
Normal		20 100%	20 100%	19 100%	12 75%	20 100%
Respiratory Rate Increased		0	0	0	4 25%	0
Blue Sclera		0	0	0	1 6%	0
DAY 19						
No. Observed		20	20	19	16	20
Normal		20 100%	20 100%	19 100%	15 94%	20 100%
Respiratory Rate Increased		0	0	0	1 6%	0
DAY 20						
No. Observed		20	20	19	16	20

^aThe high dose was reduced from 15 mg/kg/day to 10 mg/kg/day on GD12 - GD15 (the range of days reflects study stagger-start over 4 days)

^bRetinol palmitate given on GD9, and GD10 or GD12 (See Appendix 7; Study Deviations)

DEVELOPMENTAL TOXICITY (SEGMENT II)
STUDY OF WR6026 DIHYDROCHLORIDE
IN RABBITS

INCIDENCE OF OBSERVATIONS

STUDY: 173

SEX: FEMALE

PERIOD	DOSE: (mg base/kg/day) GROUP:	0	3	7	15/10 ^a	300 (mg/kg/day) ^b
		1-F	2-F	3-F	4-F	5-F
Day 20 (contd.)	Normal	20 100%	20 100%	19 100%	15 94%	20 100%
	Respiratory Rate Increased	0	0	0	1 6%	0
DAY 21	No. Observed	20	20	19	16	20
	Normal	20 100%	20 100%	19 100%	15 94%	20 100%
	Respiratory Rate Increased	0	0	0	1 6%	0
DAY 22	No. Observed	20	20	19	16	20
	Normal	20 100%	20 100%	19 100%	15 94%	20 100%
	Respiratory Rate Increased	0	0	0	1 6%	0
DAY 23	No. Observed	20	20	19	16	20
	Normal	20 100%	20 100%	19 100%	16 100%	20 100%
DAY 24	No. Observed	20	20	19	16	20
	Normal	20 100%	20 100%	19 100%	16 100%	20 100%
DAY 25	No. Observed	20	20	19	16	20
	Normal	20 100%	20 100%	19 100%	16 100%	20 100%
DAY 26	No. Observed	20	20	19	16	20
	Normal	20 100%	20 100%	19 100%	16 100%	20 100%
DAY 27	No. Observed	20	20	19	16	20
	Normal	20 100%	20 100%	19 100%	16 100%	20 100%
DAY 28	No. Observed	20	20	19	16	20
	Normal	20 100%	20 100%	19 100%	16 100%	20 100%
DAY 29	No. Observed	20	20	19	16	20
	Scheduled Sacrifice	20 100%	20 100%	19 100%	16 100%	20 100%

^aThe high dose was reduced from 15 mg/kg/day to 10 mg/kg/day on GD12 - GD15 (the range of days reflects study stagger-start over 4 days)

^bRetinol palmitate given on GD9, and GD10 or GD12 (See Appendix 7; Study Deviations)

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APPENDIX 3

Individual Maternal Body Weight and Weight Gain Data

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DEVELOPMENTAL TOXICITY (SEGMENT II)
STUDY OF WR6026 DIHYDROCHLORIDE
IN RABBITS

INDIVIDUAL BODY WEIGHTS (Kilograms)

STUDY: 173

GROUP: 1-F

SEX: FEMALE

DOSE: 0 (mg base/kg/day)

ANIMAL #	DAY 0	DAY 5	DAY 6	DAY 7	DAY 8	DAY 9	DAY 10	DAY 11	DAY 12	DAY 13	DAY 14	DAY 15
701	3.63	3.39	3.37	3.48	3.42	3.41	3.45	3.44	3.47	3.45	3.47	3.49
702	3.29	3.12	3.10	3.18	3.19	3.17	3.15	3.18	3.18	3.25	3.30	3.29
703	3.98	3.77	3.75	3.79	3.79	3.73	3.78	3.77	3.78	3.81	3.80	3.84
704	3.71	3.53	3.58	3.58	3.58	3.58	3.61	3.62	3.64	3.64	3.69	3.70
705	3.60	3.45	3.42	3.44	3.51	3.56	3.56	3.47	3.53	3.83	3.77	3.92
706	3.63	3.26	3.15	3.37	3.35	3.27	3.26	3.33	3.33	3.39	3.42	3.45
707	3.01	2.81	2.76	2.85	2.91	2.85	2.81	2.94	2.89	2.92	3.01	3.03
708	3.54	3.18	3.17	3.27	3.30	3.30	3.35	3.35	3.37	3.46	3.44	3.48
709	3.33	2.95	2.97	3.05	3.11	2.94	3.06	3.10	3.17	3.18	3.22	3.25
710	3.37	3.04	3.05	3.10	3.08	3.09	3.16	3.14	3.21	3.22	3.25	3.31
711	3.41	3.25	3.22	3.25	3.27	3.27	3.32	3.39	3.38	3.43	3.49	3.53
712	3.44	3.10	3.12	3.07	3.09	3.13	3.14	3.17	3.20	3.22	3.25	3.29
713	3.02	2.86	2.82	2.80	2.81	2.86	2.96	2.95	2.99	2.88	3.01	3.05
714	3.50	3.27	3.32	3.32	3.35	3.33	3.39	3.42	3.43	3.47	3.47	3.54
715	3.65	3.47	3.45	3.43	3.50	3.47	3.56	3.51	3.52	3.55	3.47	3.53
716	3.54	3.48	3.55	3.67	3.52	3.59	3.51	3.55	3.59	3.63	3.68	3.79
717	3.28	3.14	3.06	3.09	3.10	3.14	3.15	3.17	3.20	3.19	3.23	3.30
718	3.20	3.09	3.12	3.14	3.13	3.13	3.11	3.17	3.15	3.22	3.22	3.28
719	3.58	3.35	3.29	3.31	3.34	3.39	3.38	3.34	3.42	3.49	3.54	3.62
720	3.25	3.27	3.19	3.20	3.27	3.29	3.35	3.28	3.31	3.38	3.35	3.42
MEAN	3.45	3.24	3.22	3.27	3.28	3.28	3.30	3.31	3.34	3.38	3.40	3.46
S.D.	0.237	0.238	0.249	0.253	0.237	0.243	0.239	0.216	0.220	0.253	0.225	0.241
N	20	20	20	20	20	20	20	20	20	20	20	20

--: Data Unavailable

DEVELOPMENTAL TOXICITY (SEGMENT II)
STUDY OF WR6026 DIHYDROCHLORIDE
IN RABBITS

DRAFT

INDIVIDUAL BODY WEIGHTS (Kilograms)

STUDY: 173

GROUP: 1-F

SEX: FEMALE

DOSE: 0 (mg base/kg/day)

ANIMAL # DAY 16 DAY 17 DAY 18 DAY 24 DAY 29

701	3.48	3.53	3.52	3.65	3.70
702	3.33	3.34	3.35	3.45	3.52
703	3.83	3.84	3.84	3.89	3.99
704	3.74	3.74	3.71	3.84	3.89
705	3.75	3.68	3.88	3.88	3.88
706	3.46	3.46	3.44	3.56	3.66
707	3.05	3.05	3.05	3.09	3.20
708	3.50	3.59	3.50	3.52	3.67
709	3.33	3.29	3.26	3.37	3.41
710	3.31	3.34	3.31	3.48	3.58
711	3.57	3.55	3.53	3.56	3.59
712	3.32	3.34	3.31	3.46	3.56
713	2.98	3.04	3.03	3.07	3.22
714	3.59	3.60	3.59	3.69	3.84
715	3.44	3.56	3.51	3.59	3.72
716	3.76	3.79	3.71	3.77	3.65
717	3.29	3.33	3.30	3.40	3.46
718	3.30	3.29	3.28	3.26	3.35
719	3.59	3.53	3.54	3.63	3.65
720	3.49	3.57	3.46	3.54	3.61

MEAN	3.46	3.48	3.46	3.54	3.61
S.D.	0.226	0.220	0.228	0.229	0.210
N	20	20	20	20	20

--: Data Unavailable

DEVELOPMENTAL TOXICITY (SEGMENT II)
STUDY OF WR6026 DIHYDROCHLORIDE
IN RABBITS

DRAFT

INDIVIDUAL BODY WEIGHTS (Kilograms)

STUDY: 173

GROUP: 2-F

SEX: FEMALE

DOSE: 3 (mg base/kg/day)

ANIMAL #	DAY 0	DAY 5	DAY 6	DAY 7	DAY 8	DAY 9	DAY 10	DAY 11	DAY 12	DAY 13	DAY 14	DAY 15
721	3.54	3.42	3.34	3.38	3.35	3.39	3.39	3.42	3.44	3.50	3.52	3.57
722	3.67	3.59	3.44	3.46	3.62	3.59	3.57	3.54	3.55	3.58	3.57	3.63
723	3.68	3.47	3.46	3.48	3.50	3.48	3.50	3.45	3.57	3.58	3.60	3.59
724	3.63	3.26	3.29	3.33	3.46	3.41	3.39	3.37	3.43	3.37	3.44	3.54
725	3.64	3.54	3.57	3.55	3.63	3.69	3.61	3.60	3.67	3.67	3.70	3.68
726	3.26	2.96	2.91	2.96	3.01	3.04	3.02	3.09	3.12	3.17	3.20	3.25
727	3.34	3.05	3.08	3.18	3.22	3.15	3.21	3.20	3.29	3.29	3.40	3.46
728	3.03	2.76	2.69	2.80	2.80	2.83	2.89	2.86	2.84	2.82	2.85	2.87
729	3.38	3.11	3.14	3.19	3.15	3.21	3.28	3.28	3.34	3.35	3.40	3.38
730	3.51	3.32	3.24	3.29	3.36	3.38	3.45	3.42	3.42	3.53	3.53	3.67
731	3.52	3.28	3.26	3.30	3.35	3.37	3.40	3.42	3.40	3.40	3.45	3.57
732	3.20	2.99	3.00	2.91	2.95	2.97	2.97	3.03	3.09	3.09	3.07	3.15
733	3.42	3.14	3.21	3.18	3.24	3.26	3.18	3.24	3.26	3.34	3.29	3.43
734	3.74	3.44	3.43	3.46	3.48	3.52	3.50	3.57	3.58	3.58	3.63	3.60
735	3.35	3.13	3.10	3.15	3.19	3.19	3.22	3.34	3.32	3.38	3.42	3.45
736	3.70	3.53	3.55	3.53	3.61	3.62	3.69	3.66	3.73	3.70	3.80	3.82
737	3.20	3.16	3.19	3.16	3.12	3.16	3.20	3.23	3.17	3.25	3.29	3.33
738	3.40	3.21	3.29	3.28	3.21	3.31	3.25	3.27	3.38	3.38	3.36	3.43
739	3.05	3.06	2.93	2.98	3.05	3.07	3.12	3.12	3.13	3.12	3.21	3.18
740	3.39	3.33	3.28	3.26	3.32	3.34	3.40	3.35	3.37	3.38	3.39	3.43
MEAN	3.43	3.24	3.22	3.24	3.28	3.30	3.31	3.32	3.36	3.37	3.41	3.45
S.D.	0.213	0.221	0.225	0.211	0.231	0.226	0.216	0.202	0.216	0.215	0.220	0.219
N	20	20	20	20	20	20	20	20	20	20	20	20

--: Data Unavailable

DEVELOPMENTAL TOXICITY (SEGMENT II)
STUDY OF WR6026 DIHYDROCHLORIDE
IN RABBITS

DRAFT

INDIVIDUAL BODY WEIGHTS (Kilograms)

STUDY: 173

GROUP: 2-F

SEX: FEMALE

DOSE: 3 (mg base/kg/day)

ANIMAL # DAY 16 DAY 17 DAY 18 DAY 24 DAY 29

721	3.50	3.51	3.50	3.65	3.71
722	3.59	3.60	3.64	3.78	3.90
723	3.58	3.63	3.61	3.69	3.84
724	3.46	3.44	3.47	3.53	3.63
725	3.73	3.67	3.73	3.74	3.72
726	3.25	3.26	3.20	3.31	3.37
727	3.45	3.48	3.46	3.56	3.62
728	2.87	2.85	2.88	2.92	3.00
729	3.39	3.48	3.45	3.52	3.57
730	3.62	3.60	3.61	3.71	3.80
731	3.60	3.43	3.55	3.58	3.68
732	3.31	3.24	3.21	3.35	3.42
733	3.38	3.47	3.41	3.49	3.61
734	3.60	3.70	3.58	3.70	3.82
735	3.44	3.43	3.43	3.57	3.58
736	3.84	3.82	3.81	3.78	3.81
737	3.43	3.51	3.40	3.51	3.61
738	3.41	3.42	3.39	3.50	3.60
739	3.20	3.24	3.24	3.43	3.45
740	3.39	3.40	3.45	3.48	3.45

MEAN	3.45	3.46	3.45	3.54	3.61
S.D.	0.207	0.208	0.208	0.198	0.206
N	20	20	20	20	20

--: Data Unavailable

DRAFT

DEVELOPMENTAL TOXICITY (SEGMENT II)
STUDY OF WR6026 DIHYDROCHLORIDE
IN RABBITS

INDIVIDUAL BODY WEIGHTS (Kilograms)

STUDY: 173

GROUP: 3-F

SEX: FEMALE

DOSE: 7 (mg base/kg/day)

ANIMAL #	DAY 0	DAY 5	DAY 6	DAY 7	DAY 8	DAY 9	DAY 10	DAY 11	DAY 12	DAY 13	DAY 14	DAY 15
741	3.62	3.39	3.46	3.47	3.53	3.48	3.48	3.52	3.59	3.59	3.62	3.64
742	3.44	3.23	3.17	3.24	3.28	3.26	3.27	3.30	3.26	3.23	3.22	3.36
743	3.74	3.54	3.60	3.52	3.54	3.56	3.54	3.58	3.61	3.60	3.71	3.72
744	3.61	3.50	3.32	3.35	3.43	3.40	3.42	3.44	3.46	3.51	3.53	3.52
745	3.86	3.57	3.55	3.55	3.54	3.54	3.56	3.62	3.64	3.66	3.73	3.72
746	3.23	2.97	3.04	3.04	3.09	3.11	3.13	3.21	3.21	3.25	3.22	3.25
747	3.01	2.74	2.76	2.91	2.94	2.90	2.95	2.92	3.02	3.05	3.06	3.04
748	3.30	3.09	3.12	3.13	3.12	3.14	3.14	3.16	3.20	3.21	3.21	3.23
749	3.42	3.29	3.16	3.22	3.19	3.21	3.30	3.36	3.28	3.37	3.40	3.42
750	3.54	3.12	3.15	3.29	3.34	3.36	3.21	3.33	3.36	3.49	3.57	3.53
751	3.59	3.32	3.21	3.10	3.04	3.02	3.02	3.05	2.92	2.96	3.08	3.20
752	3.50	3.24	3.21	3.27	3.26	3.30	3.31	3.37	3.37	3.44	3.48	3.53
753	3.08	2.99	2.98	2.99	3.01	3.01	3.03	3.06	3.07	3.10	3.11	3.14
754	3.00	2.80	2.75	2.80	2.76	2.78	2.82	2.80	2.80	2.86	2.88	2.92
755	3.89	3.60	3.65	3.67	3.73	3.49	3.67	3.67	3.67	3.74	3.97	3.84
756	3.73	3.64	3.68	3.51	3.64	3.44	3.45	3.55	3.50	3.22	3.08	d
757	3.02	2.90	2.81	2.90	2.87	2.93	2.93	2.99	2.99	3.04	3.06	3.02
758	3.45	3.30	3.26	3.25	3.26	3.32	3.29	3.28	3.35	3.37	3.41	3.46
759	3.44	3.23	3.21	3.21	3.22	3.17	3.23	3.25	3.26	3.37	3.32	3.29
760	3.13	3.18	3.14	3.13	3.12	3.10	3.19	3.15	3.14	3.20	3.27	3.25
MEAN	3.43	3.23	3.21	3.23	3.25	3.23	3.25	3.28	3.29	3.31	3.35	3.37
S.D.	0.280	0.264	0.275	0.237	0.263	0.227	0.229	0.242	0.249	0.243	0.280	0.258
N	20	20	20	20	20	20	20	20	20	20	20	19

--: Data Unavailable

d: Sacrificed Moribund

DEVELOPMENTAL TOXICITY (SEGMENT II)
STUDY OF WR6026 DIHYDROCHLORIDE
IN RABBITS

INDIVIDUAL BODY WEIGHTS (Kilograms)

STUDY: 173

GROUP: 3-F

SEX: FEMALE

DOSE: 7 (mg base/kg/day)

ANIMAL # DAY 16 DAY 17 DAY 18 DAY 24 DAY 29

741	3.66	3.61	3.65	3.71	3.80
742	3.46	3.41	3.41	3.61	3.67
743	3.77	3.74	3.76	3.89	4.00
744	3.63	3.54	3.52	3.65	3.79
745	3.73	3.72	3.75	3.90	3.97
746	3.31	3.25	3.28	3.38	3.34
747	3.09	3.15	3.15	3.22	3.28
748	3.23	3.22	3.23	3.33	3.42
749	3.43	3.43	3.44	3.64	3.73
750	3.59	3.71	3.63	3.81	3.87
751	3.07	3.24	3.15	3.21	3.06
752	3.68	3.63	3.60	3.78	3.77
753	3.19	3.18	3.23	3.24	3.34
754	2.96	2.95	2.97	3.07	3.15
755	3.80	3.88	3.79	3.94	3.59
756	d	d	d	d	d
757	3.04	3.07	3.10	3.26	3.30
758	3.46	3.43	3.45	3.47	3.64
759	3.36	3.40	3.42	3.47	3.16
760	3.25	3.35	3.38	3.35	3.43

MEAN	3.41	3.42	3.42	3.52	3.54
S.D.	0.257	0.254	0.241	0.270	0.290
N	19	19	19	19	19
--: Data Unavailable			d: Sacrificed Moribund		

DEVELOPMENTAL TOXICITY (SEGMENT II)
STUDY OF WR6026 DIHYDROCHLORIDE
IN RABBITS

DRAFT

INDIVIDUAL BODY WEIGHTS (Kilograms)

STUDY: 173

GROUP: 4-F

SEX: FEMALE

DOSE: 15/10 (mg base/kg/day)^a

ANIMAL #	DAY 0	DAY 5	DAY 6	DAY 7	DAY 8	DAY 9	DAY 10	DAY 11	DAY 12	DAY 13	DAY 14	DAY 15
761	3.65	3.39	3.23	3.40	3.39	3.37	3.35	3.38	3.30	3.35	3.40	3.40
762	4.20	3.33	3.36	3.34	3.33	3.32	3.33	3.38	3.43	3.48	3.54	3.55
763	3.77	3.60	3.53	3.54	3.54	3.53	3.55	3.59	3.59	3.40	c	c
764	3.52	3.44	3.37	3.37	3.36	3.37	3.33	3.22	3.06	2.94	2.79	c
765	3.86	3.51	3.46	3.45	3.41	3.33	c	c	c	c	c	c
766	3.45	3.23	3.18	3.14	3.15	3.16	3.22	3.25	3.21	3.18	3.15	3.19
767	3.27	3.10	3.03	3.11	3.05	3.14	3.15	3.17	3.12	3.20	3.22	3.28
768	3.39	3.11	3.04	3.07	3.07	3.08	3.11	3.10	3.14	3.16	3.21	3.24
769	3.11	2.86	2.78	2.80	2.88	2.88	2.86	2.86	2.72	2.68	2.56	2.63
770	3.29	2.98	2.96	2.95	2.88	2.96	3.00	3.08	3.11	3.14	3.17	3.21
771	3.38	3.09	3.11	3.05	3.03	3.13	3.11	3.11	3.01	2.95	2.94	3.01
772	3.00	2.78	2.85	2.83	2.80	2.87	2.91	2.90	2.97	3.01	3.07	3.15
773	3.49	3.41	3.35	3.33	3.24	3.33	3.32	3.27	3.22	3.25	3.21	3.24
774	3.51	3.20	3.27	3.31	3.24	3.31	3.30	3.37	3.31	3.38	3.44	3.44
775	3.64	3.47	3.44	3.41	3.36	3.30	3.23	c	c	c	c	c
776	3.73	3.60	3.50	3.51	3.44	3.43	3.47	3.46	3.36	3.38	3.38	3.50
777	3.19	2.97	2.98	2.99	3.02	2.99	2.95	2.86	2.73	2.66	2.69	2.73
778	3.36	3.13	3.10	3.16	3.09	3.21	3.21	3.22	3.24	3.30	3.35	3.37
779	3.13	3.22	3.21	3.17	3.06	3.15	3.27	3.17	3.17	3.23	3.28	3.38
780	3.52	3.42	3.36	3.33	3.37	3.45	3.38	3.43	3.45	3.38	3.53	3.52
MEAN	3.47	3.24	3.21	3.21	3.19	3.22	3.21	3.21	3.17	3.17	3.17	3.24
S.D.	0.286	0.239	0.219	0.218	0.211	0.190	0.187	0.207	0.228	0.239	0.285	0.264
N	20	20	20	20	20	20	19	18	18	18	17	16

--: Data Unavailable

c: Animal Found Dead

^aThe high dose was reduced from 15 mg/kg/day to 10 mg/kg/day on GD12 - GD15 (the range of days reflects study stagger-start over 4 days)

DEVELOPMENTAL TOXICITY (SEGMENT II)
STUDY OF WR6026 DIHYDROCHLORIDE
IN RABBITS

INDIVIDUAL BODY WEIGHTS (Kilograms)

STUDY: 173

GROUP: 4-F

SEX: FEMALE

DOSE: 15/10 (mg base/kg/day)^a

ANIMAL # DAY 16 DAY 17 DAY 18 DAY 24 DAY 29

761	3.44	3.46	3.51	3.59	3.62
762	3.53	3.55	3.57	3.62	3.74
763	c	c	c	c	c
764	c	c	c	c	c
765	c	c	c	c	c
766	3.24	3.30	3.33	3.46	3.56
767	3.34	3.37	3.39	3.39	3.45
768	3.23	3.24	3.23	3.34	3.39
769	2.69	2.72	2.71	2.81	2.86
770	3.21	3.23	3.21	3.51	3.47
771	3.05	3.08	3.12	3.21	3.27
772	3.14	3.09	3.04	3.14	3.20
773	3.28	3.32	3.30	3.31	3.37
774	3.46	3.43	3.51	3.67	3.78
775	c	c	c	c	c
776	3.58	3.61	3.65	3.78	3.92
777	2.80	2.79	2.81	2.86	2.96
778	3.37	3.36	3.31	3.50	3.46
779	3.37	3.38	3.38	3.51	3.57
780	3.64	3.70	3.67	3.67	3.63

MEAN 3.27 3.29 3.30 3.40 3.45

S.D. 0.261 0.267 0.275 0.279 0.282

N 16 16 16 16 16

--: Data Unavailable c: Animal Found Dead

^aThe high dose was reduced from 15 mg/kg/day to 10 mg/kg/day on GD12 - GD15 (the range of days reflects study stagger-start over 4 days)

DEVELOPMENTAL TOXICITY (SEGMENT II)
STUDY OF WR6026 DIHYDROCHLORIDE
IN RABBITS

INDIVIDUAL BODY WEIGHTS (Kilograms)

STUDY: 173

GROUP: 5-F
DOSE: 300 (mg/kg/day)^a

SEX: FEMALE

ANIMAL #	DAY 0	DAY 5	DAY 6	DAY 7	DAY 8	DAY 9	DAY 10	DAY 11	DAY 12	DAY 13	DAY 14	DAY 15
781	3.57	3.56	3.38	3.47	3.42	3.50	3.48	3.47	3.51	3.53	3.61	3.63
782	3.46	3.19	3.10	3.17	3.23	3.22	3.26	3.25	3.32	3.35	3.42	3.40
783	3.81	3.66	3.61	3.71	3.65	3.73	3.68	3.65	3.78	3.81	3.82	3.85
784	3.61	3.48	3.48	3.52	3.57	3.60	3.50	3.56	3.61	3.67	3.63	3.70
785	3.84	3.34	3.26	3.32	3.31	3.34	3.33	3.27	3.32	3.43	3.45	3.44
786	3.30	3.04	2.95	3.03	3.12	3.07	3.08	3.08	3.00	3.12	3.06	3.16
787	3.24	2.93	3.05	3.04	3.02	3.11	3.09	3.15	3.10	3.15	3.27	3.28
788	3.53	3.15	3.06	3.13	3.21	3.25	3.23	3.21	3.28	3.35	3.42	3.37
789	3.14	2.93	2.86	2.98	2.98	3.00	2.98	2.95	2.99	3.07	3.04	3.14
790	3.57	3.21	3.43	3.31	3.26	3.33	3.34	3.32	3.29	3.35	3.33	3.44
791	3.44	3.27	3.21	3.25	3.32	3.34	3.35	3.34	3.32	3.38	3.41	3.44
792	3.27	3.17	3.14	3.14	3.16	3.19	3.18	3.16	3.21	3.26	3.31	3.32
793	3.70	3.44	3.40	3.36	3.38	3.42	3.42	3.43	3.42	3.46	3.51	3.54
794	3.17	2.93	2.97	2.98	3.00	2.98	2.97	3.00	3.01	3.06	3.09	3.11
795	3.29	3.09	3.12	3.13	3.14	3.17	3.18	3.20	3.18	3.14	3.25	3.28
796	3.35	3.37	3.26	3.31	3.25	3.27	3.18	3.21	3.30	3.20	3.33	3.32
797	3.73	3.58	3.53	3.54	3.52	3.53	3.55	3.58	3.61	3.53	3.26	3.69
798	3.42	3.28	3.26	3.32	3.30	3.33	3.33	3.39	3.42	3.41	3.55	3.57
799	3.14	3.12	3.12	3.03	3.12	3.18	3.01	3.04	3.06	3.16	3.14	3.22
800	3.14	2.95	2.92	2.88	2.97	2.93	3.04	3.04	3.03	3.05	3.14	3.19
MEAN	3.44	3.23	3.21	3.23	3.25	3.27	3.26	3.27	3.29	3.32	3.35	3.40
S.D.	0.227	0.228	0.214	0.219	0.194	0.211	0.201	0.201	0.224	0.211	0.208	0.207
N	20	20	20	20	20	20	20	20	20	20	20	20

--: Data Unavailable

^a Retinol palmitate given on GD9, and GD10 or GD12 (See Appendix 7; Study Deviations)

DEVELOPMENTAL TOXICITY (SEGMENT II)
STUDY OF WR6026 DIHYDROCHLORIDE
IN RABBITS

INDIVIDUAL BODY WEIGHTS (Kilograms)

STUDY: 173

GROUP: 5-F

SEX: FEMALE

DOSE: 300 (mg/kg/day)^a

ANIMAL # DAY 16 DAY 17 DAY 18 DAY 24 DAY 29

781	3.64	3.59	3.62	3.66	3.87
782	3.35	3.46	3.42	3.44	3.40
783	3.87	3.85	3.89	3.90	4.05
784	3.74	3.77	3.67	3.73	3.95
785	3.42	3.43	3.45	3.52	3.71
786	3.14	3.13	3.12	3.10	3.18
787	3.33	3.26	3.19	3.24	3.29
788	3.32	3.38	3.31	3.42	3.34
789	3.10	3.07	3.08	3.11	3.31
790	3.40	3.44	3.36	3.40	3.50
791	3.49	3.46	3.48	3.51	3.56
792	3.32	3.27	3.30	3.27	3.29
793	3.57	3.56	3.51	3.57	3.64
794	3.07	3.05	3.07	3.17	3.31
795	3.27	3.29	3.27	3.34	3.35
796	3.35	3.40	3.37	3.25	3.33
797	3.74	3.80	3.80	3.77	3.80
798	3.64	3.60	3.62	3.60	3.65
799	3.23	3.26	3.17	3.14	3.20
800	3.30	3.24	3.20	3.31	3.30

MEAN	3.41	3.42	3.40	3.42	3.50
S.O.	0.223	0.230	0.236	0.232	0.262
N	20	20	20	20	20

--: Data unavailable

^a Retinol palmitate given on GD9, and GD10 or GD12 (See Appendix 7; Study Deviations)

DRAFT

DEVELOPMENTAL TOXICITY (SEGMENT II)
STUDY OF WR6026 DIHYDROCHLORIDE
IN RABBITS

INDIVIDUAL WEIGHT GAIN (kilograms)^a

STUDY: 173

GROUP: 1-F

SEX: FEMALE

DOSE: 0 (mg base/kg/day)

ANIMAL #	DAY 7 ^b	DAY 8	DAY 9	DAY 10	DAY 11	DAY 12	DAY 13	DAY 14	DAY 15	DAY 16	DAY 17
701	0.11	-0.06	-0.01	0.04	-0.01	0.03	-0.02	0.02	0.02	-0.01	0.05
702	0.08	0.01	-0.02	-0.02	0.03	0.00	0.07	0.05	-0.01	0.04	0.01
703	0.04	0.00	-0.06	0.05	-0.01	0.01	0.03	-0.01	0.04	-0.01	0.01
704	0.00	0.00	0.00	0.03	0.01	0.02	0.00	0.05	0.01	0.04	0.00
705	0.02	0.07	0.05	0.00	-0.09	0.06	0.30	-0.06	0.15	-0.17	-0.07
706	0.22	-0.02	-0.08	-0.01	0.07	0.00	0.06	0.03	0.03	0.01	0.00
707	0.09	0.06	-0.06	-0.04	0.13	-0.05	0.03	0.09	0.02	0.02	0.00
708	0.10	0.03	0.00	0.05	0.00	0.02	0.09	-0.02	0.04	0.02	0.09
709	0.08	0.06	-0.17	0.12	0.04	0.07	0.01	0.04	0.03	0.08	-0.04
710	0.05	-0.02	0.01	0.07	-0.02	0.07	0.01	0.03	0.06	0.00	0.03
711	0.03	0.02	0.00	0.05	0.07	-0.01	0.05	0.06	0.04	0.04	-0.02
712	-0.05	0.02	0.04	0.01	0.03	0.03	0.02	0.03	0.04	0.03	0.02
713	-0.02	0.01	0.05	0.10	-0.01	0.04	-0.11	0.13	0.04	-0.07	0.06
714	0.00	0.03	-0.02	0.06	0.03	0.01	0.04	0.00	0.07	0.05	0.01
715	-0.02	0.07	-0.03	0.09	-0.05	0.01	0.03	-0.08	0.06	-0.09	0.12
716	0.12	-0.15	0.07	-0.08	0.04	0.04	0.04	0.05	0.11	-0.03	0.03
717	0.03	0.01	0.04	0.01	0.02	0.03	-0.01	0.04	0.07	-0.01	0.04
718	0.02	-0.01	0.00	-0.02	0.06	-0.02	0.07	0.00	0.06	0.02	-0.01
719	0.02	0.03	0.05	-0.01	-0.04	0.08	0.07	0.05	0.08	-0.03	-0.01
720	0.01	0.07	0.02	0.06	-0.07	0.03	0.07	-0.03	0.07	0.07	0.08
MEAN	0.05	0.01	-0.01	0.03	0.01	0.02	0.04	0.02	0.05	0.00	0.02
S.D.	0.062	0.051	0.056	0.050	0.052	0.032	0.075	0.049	0.036	0.058	0.045
N	20	20	20	20	20	20	20	20	20	20	20

--: Data Unavailable

^a Successive periods^b Baseline is day 6

DEVELOPMENTAL TOXICITY (SEGMENT II)
STUDY OF WR6026 DIHYDROCHLORIDE
IN RABBITS

DRAFT

INDIVIDUAL WEIGHT GAIN (kilograms)^a

STUDY: 173

GROUP: 1-F
DOSE: 0 (mg base/kg/day)

SEX: FEMALE

ANIMAL #	DAY 18	DAY 24	DAY 29	TOTAL GAIN
701	-0.01	0.13	0.05	0.33
702	0.01	0.10	0.07	0.42
703	0.00	0.05	0.10	0.24
704	-0.03	0.13	0.05	0.31
705	0.20	0.00	0.00	0.46
706	-0.02	0.12	0.10	0.51
707	0.00	0.04	0.11	0.44
708	-0.09	0.02	0.15	0.50
709	-0.03	0.11	0.04	0.44
710	-0.03	0.17	0.10	0.53
711	-0.02	0.03	0.03	0.37
712	-0.03	0.15	0.10	0.44
713	-0.01	0.04	0.15	0.40
714	-0.01	0.10	0.15	0.52
715	-0.05	0.08	0.13	0.27
716	-0.08	0.06	-0.12	0.10
717	-0.03	0.10	0.06	0.40
718	-0.01	-0.02	0.09	0.23
719	-0.04	0.09	0.02	0.36
720	-0.11	0.08	0.07	0.42
MEAN	-0.02	0.08	0.07	0.38
S.D.	0.060	0.051	0.063	0.111
N	20	20	20	20

--: Data Unavailable

b: Scheduled Sacrifice

^aSuccessive periods

DEVELOPMENTAL TOXICITY (SEGMENT II)
STUDY OF WR6026 DIHYDROCHLORIDE
IN RABBITS

DRAFT

INDIVIDUAL WEIGHT GAIN (kilograms)^a

STUDY: 173

GROUP: 2-F

SEX: FEMALE

DOSE: 3 (mg base/kg/day)

ANIMAL #	DAY 7 ^b	DAY 8	DAY 9	DAY 10	DAY 11	DAY 12	DAY 13	DAY 14	DAY 15	DAY 16	DAY 17
721	0.04	-0.03	0.04	0.00	0.03	0.02	0.06	0.02	0.05	-0.07	0.01
722	0.02	0.16	-0.03	-0.02	-0.03	0.01	0.03	-0.01	0.06	-0.04	0.01
723	0.02	0.02	-0.02	0.02	-0.05	0.12	0.01	0.02	-0.01	-0.01	0.05
724	0.04	0.13	-0.05	-0.02	-0.02	0.06	-0.06	0.07	0.10	-0.08	-0.02
725	-0.02	0.08	0.06	-0.08	-0.01	0.07	0.00	0.03	-0.02	0.05	-0.06
726	0.05	0.05	0.03	-0.02	0.07	0.03	0.05	0.03	0.05	0.00	0.01
727	0.10	0.04	-0.07	0.06	-0.01	0.09	0.00	0.11	0.06	-0.01	0.03
728	0.11	0.00	0.03	0.06	-0.03	-0.02	-0.02	0.03	0.02	0.00	-0.02
729	0.05	-0.04	0.06	0.07	0.00	0.06	0.01	0.05	-0.02	0.01	0.09
730	0.05	0.07	0.02	0.07	-0.03	0.00	0.11	0.00	0.14	-0.05	-0.02
731	0.04	0.05	0.02	0.03	0.02	-0.02	0.00	0.05	0.12	0.03	-0.17
732	-0.09	0.04	0.02	0.00	0.06	0.06	0.00	-0.02	0.08	0.16	-0.07
733	-0.03	0.06	0.02	-0.08	0.06	0.02	0.08	-0.05	0.14	-0.05	0.09
734	0.03	0.02	0.04	-0.02	0.07	0.01	0.00	0.05	-0.03	0.00	0.10
735	0.05	0.04	0.00	0.03	0.12	-0.02	0.06	0.04	0.03	-0.01	-0.01
736	-0.02	0.08	0.01	0.07	-0.03	0.07	-0.03	0.10	0.02	0.02	-0.02
737	-0.03	-0.04	0.04	0.04	0.03	-0.06	0.08	0.04	0.04	0.10	0.08
738	-0.01	-0.07	0.10	-0.06	0.02	0.11	0.00	-0.02	0.07	-0.02	0.01
739	0.05	0.07	0.02	0.05	0.00	0.01	-0.01	0.09	-0.03	0.02	0.04
740	-0.02	0.06	0.02	0.06	-0.05	0.02	0.01	0.01	0.04	-0.04	0.01
MEAN	0.02	0.04	0.02	0.01	0.01	0.03	0.02	0.03	0.05	0.00	0.01
S.D.	0.048	0.057	0.039	0.049	0.046	0.047	0.042	0.041	0.053	0.056	0.063
N	20	20	20	20	20	20	20	20	20	20	20

--: Data Unavailable

^a Successive periods

^b Baseline is day 6

DEVELOPMENTAL TOXICITY (SEGMENT II)
STUDY OF WR6026 DIHYDROCHLORIDE
IN RABBITS

INDIVIDUAL WEIGHT GAIN (Kilograms)^a

STUDY: 173

GROUP: 2-F

SEX: FEMALE

DOSE: 3 (mg base/kg/day)

ANIMAL #	DAY 18	DAY 24	DAY 29	TOTAL GAIN
721	-0.01	0.15	0.06	0.37
722	0.04	0.14	0.12	0.46
723	-0.02	0.08	0.15	0.38
724	0.03	0.06	0.10	0.34
725	0.06	0.01	-0.02	0.15
726	-0.06	0.11	0.06	0.46
727	-0.02	0.10	0.06	0.54
728	0.03	0.04	0.08	0.31
729	-0.03	0.07	0.05	0.43
730	0.01	0.10	0.09	0.56
731	0.12	0.03	0.10	0.42
732	-0.03	0.14	0.07	0.42
733	-0.06	0.08	0.12	0.40
734	-0.12	0.12	0.12	0.39
735	0.00	0.14	0.01	0.48
736	-0.01	-0.03	0.03	0.26
737	-0.11	0.11	0.10	0.42
738	-0.03	0.11	0.10	0.31
739	0.00	0.19	0.02	0.52
740	0.05	0.03	-0.03	0.17

MEAN -0.01 0.09 0.07 0.39

S.D. 0.056 0.054 0.048 0.110

N 20 20 20 20

--: Data Unavailable s: Scheduled Sacrifice

^aSuccessive periods

DRAFT

DEVELOPMENTAL TOXICITY (SEGMENT II)
STUDY OF WR6026 DIHYDROCHLORIDE
IN RABBITS

INDIVIDUAL WEIGHT GAIN (kilograms)^a

STUDY: 173

GROUP: 3-F

SEX: FEMALE

DOSE: 7 (mg base/kg/day)

ANIMAL #	DAY 7 ^b	DAY 8	DAY 9	DAY 10	DAY 11	DAY 12	DAY 13	DAY 14	DAY 15	DAY 16	DAY 17
741	0.01	0.06	-0.05	0.00	0.04	0.07	0.00	0.03	0.02	0.02	-0.05
742	0.07	0.04	-0.02	0.01	0.03	-0.04	-0.03	-0.01	0.14	0.10	-0.05
743	-0.08	0.02	0.02	-0.02	0.04	0.03	-0.01	0.11	0.01	0.05	-0.03
744	0.03	0.08	-0.03	0.02	0.02	0.02	0.05	0.02	-0.01	0.11	-0.09
745	0.00	-0.01	0.00	0.02	0.06	0.02	0.02	0.07	-0.01	0.01	-0.01
746	0.00	0.05	0.02	0.02	0.08	0.00	0.04	-0.03	0.03	0.06	-0.06
747	0.15	0.03	-0.04	0.05	-0.03	0.10	0.03	0.01	-0.02	0.05	0.06
748	0.01	-0.01	0.02	0.00	0.02	0.04	0.01	0.00	0.02	0.00	-0.01
749	0.06	-0.03	0.02	0.09	0.06	-0.08	0.09	0.03	0.02	0.01	0.00
750	0.14	0.05	0.02	-0.15	0.12	0.03	0.13	0.08	-0.04	0.06	0.12
751	-0.11	-0.06	-0.02	0.00	0.03	-0.13	0.04	0.12	0.12	-0.13	0.17
752	0.06	-0.01	0.04	0.01	0.06	0.00	0.07	0.04	0.05	0.15	-0.05
753	0.01	0.02	0.00	0.02	0.03	0.01	0.03	0.01	0.03	0.05	-0.01
754	0.05	-0.04	0.02	0.04	-0.02	0.00	0.06	0.02	0.04	0.04	-0.01
755	0.02	0.06	-0.24	0.18	0.00	0.00	0.07	0.23	-0.13	-0.04	0.08
756	-0.17	0.13	-0.20	0.01	0.10	-0.05	-0.28	-0.14	d	d	d
757	0.09	-0.03	0.06	0.00	0.06	0.00	0.05	0.02	-0.04	0.02	0.03
758	-0.01	0.01	0.06	-0.03	-0.01	0.07	0.02	0.04	0.05	0.00	-0.03
759	0.00	0.01	-0.05	0.06	0.02	0.01	0.11	-0.05	-0.03	0.07	0.04
760	-0.01	-0.01	-0.02	0.09	-0.04	-0.01	0.06	0.07	-0.02	0.00	0.10
MEAN	0.02	0.02	-0.02	0.02	0.03	0.00	0.03	0.03	0.01	0.03	0.01
S.D.	0.076	0.046	0.076	0.062	0.042	0.052	0.082	0.074	0.059	0.060	0.069
N	20	20	20	20	20	20	20	20	19	19	19

---: Data Unavailable

d: Sacrificed Moribund

^a Successive periods^b Baseline is day 6

DRAFT

DEVELOPMENTAL TOXICITY (SEGMENT II)
STUDY OF WR6026 DIHYDROCHLORIDE
IN RABBITS

INDIVIDUAL WEIGHT GAIN (Kilograms)^a

STUDY: 173

GROUP: 3-F
DOSE: 7 (mg base/kg/day)

SEX: FEMALE

ANIMAL #	OAY 18	OAY 24	OAY 29	TOTAL GAIN
741	0.04	0.06	0.09	0.34
742	0.00	0.20	0.06	0.50
743	0.02	0.13	0.11	0.40
744	-0.02	0.13	0.14	0.47
745	0.03	0.15	0.07	0.42
746	0.03	0.10	-0.04	0.30
747	0.00	0.07	0.06	0.52
748	0.01	0.10	0.09	0.30
749	0.01	0.20	0.09	0.57
750	-0.08	0.18	0.06	0.72
751	-0.09	0.06	-0.15	-0.15
752	-0.03	0.18	-0.01	0.56
753	0.05	0.01	0.10	0.36
754	0.02	0.10	0.08	0.40
755	-0.09	0.15	-0.35	-0.06
756	d	d	d	--
757	0.03	0.16	0.04	0.49
758	0.02	0.02	0.17	0.38
759	0.02	0.05	-0.31	-0.05
760	0.03	-0.03	0.08	0.29
MEAN	0.00	0.11	0.02	0.36
S.O.	0.043	0.067	0.141	0.225
N	19	19	19	19

--: Data Unavailable

b: Scheduled Sacrifice

d: Sacrificed Moribund

^aSuccessive periods

DEVELOPMENTAL TOXICITY (SEGMENT II)
STUDY OF WR6026 DIHYDROCHLORIDE
IN RABBITS

INDIVIDUAL WEIGHT GAIN (Kilograms)^a

STUDY: 173

GROUP: 4-F

SEX: FEMALE

DOSE: 15/10 (mg base/kg/day)^d

ANIMAL #	DAY 7 ^b	DAY 8	DAY 9	DAY 10	DAY 11	DAY 12	DAY 13	DAY 14	DAY 15	DAY 16	DAY 17
761	0.17	-0.01	-0.02	-0.02	0.03	-0.08	0.05	0.05	0.00	0.04	0.02
762	-0.02	-0.01	-0.01	0.01	0.05	0.05	0.05	0.06	0.01	-0.02	0.02
763	0.01	0.00	-0.01	0.02	0.04	0.00	-0.19	c	c	c	c
764	0.00	-0.01	0.01	-0.04	-0.11	-0.16	-0.12	-0.15	c	c	c
765	-0.01	-0.04	-0.08	c	c	c	c	c	c	c	c
766	-0.04	0.01	0.01	0.06	0.03	-0.04	-0.03	-0.03	0.04	0.05	0.06
767	0.08	-0.06	0.09	0.01	0.02	-0.05	0.08	0.02	0.06	0.06	0.03
768	0.03	0.00	0.01	0.03	-0.01	0.04	0.02	0.05	0.03	-0.01	0.01
769	0.02	0.08	0.00	-0.02	0.00	-0.14	-0.04	-0.12	0.07	0.06	0.03
770	-0.01	-0.07	0.08	0.04	0.08	0.03	0.03	0.03	0.04	0.00	0.02
771	-0.06	-0.02	0.10	-0.02	0.00	-0.10	-0.06	-0.01	0.07	0.04	0.03
772	-0.02	-0.03	0.07	0.04	-0.01	0.07	0.04	0.06	0.08	-0.01	-0.05
773	-0.02	-0.09	0.09	-0.01	-0.05	-0.05	0.03	-0.04	0.03	0.04	0.04
774	0.04	-0.07	0.07	-0.01	0.07	-0.06	0.07	0.06	0.00	0.02	-0.03
775	-0.03	-0.05	-0.06	-0.07	c	c	c	c	c	c	c
776	0.01	-0.07	-0.01	0.04	-0.01	-0.10	0.02	0.00	0.12	0.08	0.03
777	0.01	0.03	-0.03	-0.04	-0.09	-0.13	-0.07	0.03	0.04	0.07	-0.01
778	0.06	-0.07	0.12	0.00	0.01	0.02	0.06	0.05	0.02	0.00	-0.01
779	-0.04	-0.11	0.09	0.12	-0.10	0.00	0.06	0.05	0.10	-0.01	0.01
780	-0.03	0.04	0.08	-0.07	0.05	0.02	-0.07	0.15	-0.01	0.12	0.06
MEAN	0.01	-0.03	0.03	0.00	0.00	-0.04	0.00	0.02	0.04	0.03	0.02
S.O.	0.052	0.048	0.059	0.046	0.056	0.070	0.074	0.071	0.037	0.040	0.030
N	20	20	20	19	18	18	18	17	16	16	16

--: Data Unavailable

c: Animal Found Dead

^a Successive periods

^b Baseline is day 6

^d The high dose was reduced from 15 mg/kg/day to 10 mg/kg/day on G012 - G015 (the range of days reflects study stagger-start over 4 days)

DEVELOPMENTAL TOXICITY (SEGMENT II)
STUDY OF WR6026 DIHYDROCHLORIDE
IN RABBITS

INDIVIDUAL WEIGHT GAIN (kilograms)^a

STUDY: 173

GROUP: 4-F

SEX: FEMALE

DOSE: 15/10 (mg base/kg/day)^d

ANIMAL #	DAY 18	DAY 24	DAY 29	TOTAL GAIN
761	0.05	0.08	0.03	0.39
762	0.02	0.05	0.12	0.38
763	c	c	c	--
764	c	c	c	--
765	c	c	c	--
766	0.03	0.13	0.10	0.38
767	0.02	0.00	0.06	0.42
768	-0.01	0.11	0.05	0.35
769	-0.01	0.10	0.05	0.08
770	-0.02	0.30	-0.04	0.51
771	0.04	0.09	0.06	0.16
772	-0.05	0.10	0.06	0.35
773	-0.02	0.01	0.06	0.02
774	0.08	0.16	0.11	0.51
775	c	c	c	--
776	0.04	0.13	0.14	0.42
777	0.02	0.05	0.10	-0.02
778	-0.05	0.19	-0.04	0.36
779	0.00	0.13	0.06	0.36
780	-0.03	0.00	-0.04	0.27
MEAN	0.01	0.10	0.06	0.31
S.D.	0.037	0.077	0.056	0.163
N	16	16	16	16

--: Data Unavailable

b: Scheduled Sacrifice

c: Animal Found Dead

^a Successive periods

^dThe high dose was reduced from 15 mg/kg/day to 10 mg/kg/day on GD12 - GD15 (the range of days reflects study stagger-start over 4 days)

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DEVELOPMENTAL TOXICITY (SEGMENT II)
STUDY OF WR6026 DIHYDROCHLORIDE
IN RABBITS

INDIVIDUAL WEIGHT GAIN (Kilograms)^a

STUDY: 173

GROUP: 5-F

SEX: FEMALE

DOSE: 300 (mg/kg/day)^c

ANIMAL #	DAY 7 ^b	DAY 8	DAY 9	DAY 10	DAY 11	DAY 12	DAY 13	DAY 14	DAY 15	DAY 16	DAY 17
781	0.09	-0.05	0.08	-0.02	-0.01	0.04	0.02	0.08	0.02	0.01	-0.05
782	0.07	0.06	-0.01	0.04	-0.01	0.07	0.03	0.07	-0.02	-0.05	0.11
783	0.10	-0.06	0.08	-0.05	-0.03	0.13	0.03	0.01	0.03	0.02	-0.02
784	0.04	0.05	0.03	-0.10	0.06	0.05	0.06	-0.04	0.07	0.04	0.03
785	0.06	-0.01	0.03	-0.01	-0.06	0.05	0.11	0.02	-0.01	-0.02	0.01
786	0.08	0.09	-0.05	0.01	0.00	-0.08	0.12	-0.06	0.10	-0.02	-0.01
787	-0.01	-0.02	0.09	-0.02	0.06	-0.05	0.05	0.12	0.01	0.05	-0.07
788	0.07	0.08	0.04	-0.02	-0.02	0.07	0.07	0.07	-0.05	-0.05	0.06
789	0.12	0.00	0.02	-0.02	-0.03	0.04	0.08	-0.03	0.10	-0.04	-0.03
790	-0.12	-0.05	0.07	0.01	-0.02	-0.03	0.06	-0.02	0.11	-0.04	0.04
791	0.04	0.07	0.02	0.01	-0.01	-0.02	0.06	0.03	0.03	0.05	-0.03
792	0.00	0.02	0.03	-0.01	-0.02	0.05	0.05	0.05	0.01	0.00	-0.05
793	-0.04	0.02	0.04	0.00	0.01	-0.01	0.04	0.05	0.03	0.03	-0.01
794	0.01	0.02	-0.02	-0.01	0.03	0.01	0.05	0.03	0.02	-0.04	-0.02
795	0.01	0.01	0.03	0.01	0.02	-0.02	-0.04	0.11	0.03	-0.01	0.02
796	0.05	-0.06	0.02	-0.09	0.03	0.09	-0.10	0.13	-0.01	0.03	0.05
797	0.01	-0.02	0.01	0.02	0.03	0.03	-0.08	-0.27	0.43	0.05	0.06
798	0.06	-0.02	0.03	0.00	0.06	0.03	-0.01	0.14	0.02	0.07	-0.04
799	-0.09	0.09	0.06	-0.17	0.03	0.02	0.10	-0.02	0.08	0.01	0.03
800	-0.04	0.09	-0.04	0.11	0.00	-0.01	0.02	0.09	0.05	0.11	-0.06
MEAN	0.03	0.02	0.03	-0.02	0.01	0.02	0.04	0.03	0.05	0.01	0.00
S.D.	0.063	0.052	0.038	0.057	0.033	0.050	0.057	0.091	0.098	0.044	0.048
N	20	20	20	20	20	20	20	20	20	20	20

---: Data Unavailable

^a Successive periods^b Baseline is day 6^c Retinol palmitate given on GD9, and GD10 or GD12 (See Appendix 7; Study Deviations)

DEVELOPMENTAL TOXICITY (SEGMENT II)
STUDY OF WR6026 DIHYDROCHLORIDE
IN RABBITS

INDIVIDUAL WEIGHT GAIN (kilograms) ^a

STUDY: 173

GROUP: 5-F
DOSE: 300 (mg/kg/day) ^c

SEX: FEMALE

ANIMAL #	DAY 18	DAY 24	DAY 29	TOTAL GAIN
781	0.03	0.04	0.21	0.49
782	-0.04	0.02	-0.04	0.30
783	0.04	0.01	0.15	0.44
784	-0.10	0.06	0.22	0.47
785	0.02	0.07	0.19	0.45
786	-0.01	-0.02	0.08	0.23
787	-0.07	0.05	0.05	0.24
788	-0.07	0.11	-0.08	0.28
789	0.01	0.03	0.20	0.45
790	-0.08	0.04	0.10	0.07
791	0.02	0.03	0.05	0.35
792	0.03	-0.03	0.02	0.15
793	-0.05	0.06	0.07	0.24
794	0.02	0.10	0.14	0.34
795	-0.02	0.07	0.01	0.23
796	-0.03	-0.12	0.08	0.07
797	0.00	-0.03	0.03	0.27
798	0.02	-0.02	0.05	0.39
799	-0.09	-0.03	0.06	0.08
800	-0.04	0.11	-0.01	0.38
MEAN	-0.02	0.03	0.08	0.30
S.D.	0.045	0.057	0.084	0.134
N	20	20	20	20
--: Data Unavailable b: Scheduled Sacrifice				

^a Successive periods

^c Retinol palmitate given on GD9, and GD10 or GD12 (See Appendix 7; Study Deviations)

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APPENDIX 4

Individual Maternal Food Consumption Data

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DEVELOPMENTAL TOXICITY (SEGMENT II)
STUDY OF WR6026 DIHYDROCHLORIDE
IN RABBITS

INDIVIDUAL DAILY FOOD CONSUMPTION (Grams)

STUDY: 173

GROUP: 1-F

SEX: FEMALE

DOSE: 0 (mg base/kg/day)

ANIMAL #	DAY 8	DAY 10	DAY 12	DAY 15	DAY 18	DAY 24	DAY 29
----------	-------	--------	--------	--------	--------	--------	--------

701	130	130	130	130	130	130	130
702	130	130	130	130	130	130	130
703	130	130	130	130	130	130	130
704	130	130	130	130	130	130	130
705	130	130	130	130	130	130	130
706	130	130	130	130	130	130	130
707	130	130	130	130	130	130	130
708	130	130	130	130	130	130	130
709	130	130	130	130	130	130	130
710	130	130	130	130	130	130	130
711	130	130	130	130	130	130	130
712	130	130	130	130	130	130	130
713	130	130	130	130	130	130	130
714	130	130	130	130	130	130	130
715	130	130	130	130	110	130	130
716	130	130	130	130	130	130	130
717	130	130	130	130	130	130	130
718	130	130	130	130	130	130	130
719	130	130	130	130	130	130	130
720	130	130	130	130	130	130	130

MEAN	130	130	130	130	129	130	130
S.D.	0.0	0.0	0.0	0.0	4.5	0.0	0.0
N	20	20	20	20	20	20	20

---: Data Unavailable

DEVELOPMENTAL TOXICITY (SEGMENT II)
 STUDY OF WR6026 DIHYDROCHLORIDE
 IN RABBITS

INDIVIDUAL DAILY FOOD CONSUMPTION (Grams)

STUDY: 173

GROUP: 2-F

SEX: FEMALE

DOSE: 3 (mg base/kg/day)

ANIMAL #	DAY 8	DAY 10	DAY 12	DAY 15	DAY 18	DAY 24	DAY 29
721	130	130	130	130	130	130	130
722	130	130	130	130	130	130	130
723	130	130	130	130	130	130	130
724	130	130	130	130	130	130	130
725	130	130	130	130	130	130	130
726	130	130	130	130	130	130	130
727	130	130	130	130	130	130	130
728	130	130	130	130	130	130	130
729	130	130	130	130	130	130	130
730	130	130	130	130	130	130	130
731	130	130	130	130	130	130	130
732	130	130	130	130	130	130	130
733	130	130	130	130	130	130	130
734	130	130	130	130	130	130	130
735	130	130	130	130	130	130	130
736	130	130	130	130	130	130	130
737	130	130	130	130	130	130	130
738	130	130	130	130	130	130	130
739	130	130	130	130	130	130	130
740	130	130	130	130	130	130	130
MEAN	130	130	130	130	130	130	130
S.D.	0.0	0.0	0.0	0.0	0.0	0.0	0.0
N	20	20	20	20	20	20	20

---: Data Unavailable

DEVELOPMENTAL TOXICITY (SEGMENT II)
STUDY OF WR6026 DIHYDROCHLORIDE
IN RABBITS

INDIVIDUAL DAILY FOOD CONSUMPTION (Grams)

STUDY: 173

GROUP: 3-F

SEX: FEMALE

DOSE: 7 (mg base/kg/day)

ANIMAL # DAY 8 DAY 10 DAY 12 DAY 15 DAY 18 DAY 24 DAY 29

741	130	130	130	130	130	130	130
742	130	130	63	108	130	130	130
743	130	130	130	130	130	130	130
744	130	130	130	130	130	130	130
745	130	130	130	130	130	130	130
746	130	130	130	130	130	130	130
747	130	130	130	130	130	130	130
748	130	130	130	130	130	130	130
749	130	130	130	130	130	130	130
750	130	130	130	130	130	130	130
751	0	13	57	130	130	130	96
752	130	130	130	130	130	130	130
753	130	130	130	130	130	130	130
754	130	130	130	130	130	130	130
755	130	130	130	130	130	130	130
756	130	86	105	d	d	d	d
757	130	130	130	130	130	130	75
758	130	130	130	130	130	130	130
759	130	130	130	130	130	130	130
760	130	130	130	130	130	130	130

MEAN	124	122	122	129	130	130	125
S.D.	29.1	27.5	21.9	5.0	0.0	0.0	14.5
N	20	20	20	19	19	19	19

--: Data Unavailable

d: Sacrificed Moribund

DEVELOPMENTAL TOXICITY (SEGMENT II)
STUDY OF WR6026 DIHYDROCHLORIDE
IN RABBITS

INDIVIDUAL DAILY FOOD CONSUMPTION (Grams)

STUDY: 173

GROUP: 4-F

SEX: FEMALE

DOSE: 15/10 (mg base/kg/day)^a

ANIMAL #	DAY 8	DAY 10	DAY 12	DAY 15	DAY 18	DAY 24	DAY 29
761	130	130	76	130	130	130	130
762	130	130	130	130	130	130	130
763	130	130	130	c	c	c	c
764	53	130	4	--	c	c	c
765	130	--	c	c	c	c	c
766	130	130	130	130	130	130	130
767	130	130	130	130	130	130	130
768	130	130	130	130	130	130	130
769	130	130	0	30	130	130	130
770	130	130	130	130	130	130	130
771	92	130	65	130	130	130	130
772	130	130	106	125	130	130	130
773	130	130	91	130	130	130	130
774	130	130	130	130	130	130	130
775	130	14	c	c	c	c	c
776	130	130	53	130	130	130	130
777	130	107	0	56	130	130	130
778	130	130	130	130	130	130	130
779	130	130	130	130	130	130	130
780	130	130	130	130	130	130	130

MEAN	124	123	94	119	130	130	130
S.D.	18.8	26.8	49.5	30.0	0.0	0.0	0.0
N	20	19	18	16	16	16	16

--: Data Unavailable

c: Animal Found Dead

^aThe high dose was reduced from 15 mg/kg/day to 10 mg/kg/day on GD12 - GD15 (the range of days reflects study stagger-start over 4 days)

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DEVELOPMENTAL TOXICITY (SEGMENT II)
STUDY OF WR6026 DIHYDROCHLORIDE
IN RABBITS

INDIVIDUAL DAILY FOOD CONSUMPTION (Grams)

STUDY: 173

GROUP: 5-F

SEX: FEMALE

DOSE: 300 (mg/kg/day)^a

ANIMAL #	DAY 8	DAY 10	DAY 12	DAY 15	DAY 18	DAY 24	DAY 29
781	130	130	130	130	130	130	130
782	130	130	130	130	130	130	130
783	130	130	130	130	130	130	130
784	130	130	130	130	130	130	130
785	130	130	130	130	130	130	130
786	130	130	130	130	130	130	130
787	130	130	130	130	130	130	130
788	130	130	130	130	130	130	130
789	130	130	130	130	130	130	130
790	130	130	130	130	130	130	130
791	130	130	130	130	130	130	130
792	130	130	130	130	130	130	130
793	130	130	130	130	130	130	130
794	130	130	130	130	130	130	130
795	130	130	130	130	130	130	130
796	130	130	130	130	130	130	130
797	130	130	130	130	130	130	130
798	130	130	130	130	130	130	130
799	130	130	130	130	130	130	130
800	130	130	130	130	130	130	130
MEAN	130	130	130	130	130	130	130
S.D.	0.0	0.0	0.0	0.0	0.0	0.0	0.0
N	20	20	20	20	20	20	20

---: Data Unavailable

^a Retinol palmitate given on GD9, and GD10 or GD12 (See Appendix 7; Study Deviations)

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APPENDIX 5
Teratology Report



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TERATOLOGY REPORT

FOR

DEVELOPMENTAL TOXICITY (SEGMENT II) STUDY
OF WR6026 DIHYDROCHLORIDE IN RABBITS

UIC/TRL STUDY NUMBER: 173

PREPARED FOR

TOXICOLOGY RESEARCH LABORATORY (TRL)
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I. QUALITY ASSURANCE STATEMENT

This teratology project has been inspected and audited by the PAI Quality Assurance Unit (QAU) as required by the Good Laboratory Practice (GLP) regulations promulgated by the U.S. Food and Drug Administration. The following table is a record of the inspections/audits performed and reported by the QAU.

<u>Date of Inspection</u>	<u>Phase Inspected</u>	<u>Date Findings Reported to Management/ Study Teratologist</u>
05/24/95	Skeletal Examination	05/24/95
06/08-09/95	Individual Animal Data (Raw Data)	06/15/95
06/09-14/95	Individual Animal Data (Data Entry)	06/15/95
06/14/95	Draft Teratology Report	06/15/95
06/21/95	Second Draft Teratology Report	06/21/95
06/26/95	Third Draft Teratology Report	06/26/95

Patricia L. Bussard
Quality Assurance Auditor

June 26, 1995

Date

TRL Study No. 173
DEVELOPMENTAL TOXICITY (SEGMENT II) STUDY OF WR6026 DIHYDROCHLORIDE IN RABBITS

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Developmental Toxicity (Segment II) Study of WR6026 Dihydrochloride in Rabbits

II. MATERIALS AND METHODS

A. Cesarean Section

On gestation day 29, all surviving rabbits were euthanized in a random order by intravenous injection of sodium pentobarbital. The abdominal and thoracic cavities were opened by a ventral midline incision and the uterus and ovaries were removed from the body. A gross necropsy was then performed and abnormalities were recorded. Gross findings did not indicate the necessity of retaining any tissue samples containing gross lesions for possible histopathological examination. Following the gross necropsy examination, the carcass of each dam was discarded.

The uterus was examined and weighed. For gravid females, the number of corpora lutea on each ovary was recorded and the ovaries were discarded after evaluation. The uterus was opened and the development of the fetuses was classified using the following criteria:

- Viable fetus: a term fetus which responds to stimuli.
- Nonviable fetus: a term fetus which did not respond to stimuli *in utero* or was not breathing.
- Early resorption: an implantation for which it was not grossly evident that organogenesis had occurred.
- Late resorption: an implantation for which it was grossly evident that organogenesis had occurred. A fetus with autolysis was considered a late resorption.

The number and location of fetuses, early resorption(s), late resorption(s) and their uterine position were documented using the following procedure. All implantation sites were numbered in consecutive fashion per uterine horn beginning with the left distal horn and proceeding to the cervix and then similarly for the right uterine horn beginning with the distal end and proceeding to the cervix. Uteri with no evidence of pregnancy were placed in 10% aqueous ammonium sulfide solution for detection of possible implantation sites.

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B. Fetal Evaluation

1. External Examination

A detailed examination of each fetus was conducted to include the eyes, palate, head shape, extremities and general body integument. The fetuses were then weighed.

2. Visceral Examination

Each fetus was euthanized by intraperitoneal injection of a 40% sodium pentobarbital solution (approximately 0.4 ml/fetus) and then dissected. The abdominal, thoracic and cranial cavities were opened and the internal organs were examined as described by Staples (1974). During the examination, the fetal sex was determined. The fetuses were then individually tagged.

3. Skeletal Examination

Following the visceral examination, the fetuses were retained in 95% alcohol for skeletal examination. These fetuses were macerated in 2% potassium hydroxide, stained with Alizarin Red S and cleared with glycerin (Dawson, 1926). The fetuses were then examined for skeletal formation and ossification.

C. Statistical Analyses

The incidences or the means and standard deviations of the maternal and fetal observations were calculated. Gravid uterus weights and fetal body weights were analyzed by one-way analysis of variance (ANOVA). If a significant F ratio was obtained ($p \leq 0.05$), Dunnett's test was used for pair-wise comparisons of each treated group to the vehicle control group.

The numbers of early and late resorptions, nonviable fetuses, viable fetuses, total implantation sites and corpora lutea and the percent preimplantation loss, post-implantation loss and total loss/litter were compared across groups using the Kruskal-Wallis nonparametric ANOVA test. If a significant effect occurred ($p \leq 0.05$), the Wilcoxon (Mann-Whitney U) test was used for pair-wise comparisons of each treated group to the vehicle control group.

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Calculations were as follows:

$$\text{Pre-implantation loss \%} = \frac{\#Corpora\ lutea - \#Implants}{\#Corpora\ Lutea} \times 100$$

$$\text{Post-implantation loss \%} = \frac{\#Implants - \#Viable\ fetuses}{\#Implants} \times 100$$

$$\text{Total loss/litter \%} = \frac{\#Corpora\ lutea - \#Viable\ fetuses}{\#Corpora\ Lutea} \times 100$$

Male to female fetal sex ratios were compared using the Chi-square test. The incidences of malformations and variations were compared using the Fisher's exact test with the litter as the experimental unit. The total number of litters with external, visceral and skeletal malformations as well as the total number of litters with malformations and variations were also statistically compared. The percent of fetuses and litters with malformations and variations were calculated and reported, however, these data were not statistically analyzed.

Statistical analyses of the cesarean section and fetal morphological examination data were performed using an IBMTM compatible computer with SAS computer programs (SAS/STAT User's Guide, 1989).

III. RESULTS

A. Survival and Pregnancy

Table 1 (Summary Data)

Four females in the 15/10 mg base/kg/day group were found dead during the study. The deaths occurred between gestation days 8-14, generally prior to the reduction in the dosage level from 15 to 10 mg base/kg/day, and were considered the result of WR6026 Dihydrochloride administration. One female in the 7 mg base/kg/day group was sacrificed moribund on gestation day 8 due to back trauma. Loss in body weight and bloody discharge were considered secondary to the injury. The death was not considered treatment-related. All other animals survived to scheduled Cesarean section. The pregnancy rate was 100% in the vehicle control, and the 7 and 15/10 mg base/kg/day groups, 90% in the 3 mg base/kg/day group, and 95% in the positive control group.

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B. Maternal Gross Necropsy

Table 2 (Summary Data)
Appendix A (Individual Data)

No treatment-related changes were observed in the 3, 7 and 15/10 mg base/kg/day groups or in the positive control group.

C. Cesarean Section Data

Table 3 (Summary Data)
Appendices B and C (Individual Data)

There were no biologically meaningful differences between the vehicle control and the WR6026 Dihydrochloride groups in the cesarean section parameters measured, including the numbers of corpora lutea, implantation sites, viable and nonviable fetuses, early and late resorptions, pre-implantation loss, post-implantation loss, total loss/litter, fetal sex ratios, and gravid uterus and fetal weights. An incidental but statistically significant increase in the mean number of viable fetuses occurred at the 3 mg base/kg/day level. Treatment-related differences noted in the positive control group included statistically significant increases in the numbers of early resorptions, and the percent post-implantation loss, the percent total loss/litter and a corresponding nonstatistically significant decrease in the mean number of viable fetuses. In addition, the gravid uterus weight was slightly reduced in the positive control group. The reduction in the uterus weight was attributable to the reduced number of viable fetuses in the group.

D. Fetal Morphological Observations

Tables 4-7 (Summary Data)
Appendix D (Individual Data)

No apparent treatment-related malformations or developmental variations were observed at the 3 or 7 mg base/kg/day levels. In the 15/10 mg base/kg/day group, the number of litters with vertebral anomalies and the number of litters with skeletal malformations were slightly increased as compared to the control group. This occurrence was due to two litters (#766 and #776) containing fetuses with various vertebral anomalies. The increase was not statistically significant. An incidental but statistically significant increase in the number of litters with sternebrae #5-#6 unossified occurred in the 3 mg base/kg/day group. In the positive control group, statistical increases were observed in the number of litters with external, visceral, and skeletal malformations. The external malformations primarily involved structures of the head

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involved structures of the head including the mouth, jaws, palate, pinnae and tail. In addition, a significant increase in the occurrence of additional structures in the facial region was noted. The visceral malformations primarily included heart/great vessel and kidney/ureter anomalies. Skeletal malformations included skull, vertebral, caudal vertebrae and hyoid anomalies. The incidences of two developmental variations (involving the major blood vessels and gallbladder) were also increased in the positive control group compared to the vehicle control group.

IV. DISCUSSION AND CONCLUSIONS

This study was conducted to evaluate the embryo/fetal toxicity and the teratogenic potential of WR6026 Dihydrochloride in rabbits.

Treatment-related mortality occurred for four females from the 15/10 mg base/kg/day group. One female in the 7 mg base/kg/day group was sacrificed moribund apparently due to an accidental injury. Overall pregnancy and maternal gross necropsy findings were not affected by treatment with WR6026 Dihydrochloride. Cesarean section data were comparable between the vehicle control and the 3, 7 and 15/10 mg base/kg/day groups. Similarly, no biologically meaningful differences were noted in the fetal morphological examination data from the 3 and 7 mg base/kg/day WR6026 Dihydrochloride treated groups. At the 15/10 mg base/kg/day level, two litters were observed with fetuses having vertebral anomalies. No statistically significant increases in the number of litters with skeletal malformations resulted. However, since the malformations observed for the fetuses from both litters were of a similar nature, it is unclear if the vertebral anomalies were or were not a result of treatment with WR6026 Dihydrochloride. It should be noted that the dose level at which the increased number of vertebral malformations was observed also produced overt maternal toxicity including death.

The use of Vitamin A (Retinol Palmitate) as a positive control agent was effective in producing a teratogenic response. A dose level of 300 mg/kg/day, administered on gestation days 9 and 10, or gestation days 9 and 12 for 5 of the 20 animals (study deviation), resulted in increased post-implantation loss and percent total loss/litter as characterized by an increase in early resorptions and a decrease in viable fetuses. A decrease in gravid uterus weights associated with the lower number of surviving fetuses was also observed. The incidences of external, visceral and skeletal malformations were significantly increased. Salient findings were primarily related to the structures of the head (including the skull and hyoid), kidneys and ureters, and vertebral column (including the tail). The results seen for the 5 animals which received the second dose of Vitamin A on gestation day 12 instead of gestation day 10 were similar to those seen for the other positive control animals.

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Study No. 173

In conclusion, maternal toxicity was produced in the 15/10 mg base/kg/day group. No evidence of embryo/fetal toxicity or teratogenicity was produced at the 3 and 7 mg base/kg/day levels. Teratologic results at the maternally lethal dose of 15/10 mg base/kg/day were equivocal as vertebral malformations were observed in two litters. The no-effect level for developmental toxicity of WR6026 Dihydrochloride in rabbits was at least 7 mg base/kg/day and possibly 15/10 mg base/kg/day. Results of the positive control group demonstrated that the procedures utilized in the conduct of this study were sufficiently sensitive to identify potential developmental toxicants.

Date:

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V. REFERENCES

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TABLE 1

UIC/TRL STUDY NO.: 173 DEVELOPMENTAL TOXICITY (SEGMENT II) STUDY OF WR6026 DIHYDROCHLORIDE IN RABBITS

SUMMARY OF PREGNANCY STATUS

GROUP: DOSE LEVEL (MG BASE/KG/DAY):	1		2		3		4		5	
	No.	%	No.	%	No.	%	No.	%	No.	%
FEMALES ON STUDY	20		20		20		20		20	
FOUND DEAD/EUTHANIZED	0	0.0	0	0.0	1	5.0	4	20.0	0	0.0
PREMATURE DELIVERY/ABORTION	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0
EXAMINED AT CESAREAN SECTION	20	100.0	20	100.0	19	95.0	16	80.0	20	100.0
NONGRAVID	0	0.0	2	10.0	0	0.0	0	0.0	1	5.0
GRAVID	20	100.0	18	90.0	19	100.0	16	100.0	19	95.0
WITH TOTAL RESORPTIONS	0	0.0	0	0.0	0	0.0	0	0.0	3	15.8
WITH LIVE FETUSES	20	100.0	18	100.0	19	100.0	16	100.0	16	84.2
TOTAL GRAVID FEMALES	20	100.0	18	90.0	20	100.0	20	100.0	19	95.0

* DUE TO MORTALITY, THE HIGH DOSE WAS REDUCED FROM 15 MG BASE/KG/DAY TO 10 MG BASE/KG/DAY ON GESTATION DAYS 12-15 (THE RANGE OF DAYS REFLECTS STUDY STAGGER-START OVER 4 DAYS).

^b RETINOL PALMITATE (75,000 I.U./KG/DAY ON GESTATION DAYS 9 AND 10, OR 9 AND 12 FOR 5 OF 20 ANIMALS - STUDY DEVIATION).

TABLE 2

UIC/TRL STUDY NO.: 173 DEVELOPMENTAL TOXICITY (SEGMENT II) STUDY OF WR6026 DIHYDROCHLORIDE IN RABBITS
SUMMARY OF GROSS NECROPSY OBSERVATIONS

	GROUP: DOSE LEVEL (MG BASE/KG/DAY):				
	1	2	3	4	5
	0	3	7	15/10 ^a	300 MG/KG/DAY ^b
NUMBER OF FEMALES EXAMINED AT THE SCHEDULED GESTATION DAY 29 CESAREAN SECTION	20	20	19 ^c	16 ^c	20
NO ABNORMALITIES DETECTED	20	19	19	16	20
NONGRAVID - AMMONIUM SULFIDE TEST NEGATIVE	0	2	0	0	1
GRAVID - AMMONIUM SULFIDE TEST POSITIVE	0	0	0	0	0
OVIDUCT - CYST	0	1	0	0	0

^a DUE TO MORTALITY, THE HIGH DOSE WAS REDUCED FROM 15 MG BASE/KG/DAY TO 10 MG BASE/KG/DAY ON GESTATION DAYS 12-15 (THE RANGE OF DAYS REFLECTS STUDY STAGGER-START OVER 4 DAYS).

^b RETINOL PALMITATE (75,000 I.U./KG/DAY ON GESTATION DAYS 9 AND 10, OR 9 AND 12 FOR 5 OF 20 ANIMALS - STUDY DEVIATION).

^c DOES NOT INCLUDE FEMALES WHICH DIED EARLY (SEE APPENDIX A FOR INDIVIDUAL FINDINGS).

TABLE 3

UIC/TRL STUDY NO.: 173 DEVELOPMENTAL TOXICITY (SEGMENT II) STUDY OF WR6026 DIHYDROCHLORIDE IN RABBITS

SUMMARY OF CESAREAN SECTION DATA

GROUP: DOSE LEVEL (MG BASE/KG/DAY):		1	2	3	4	5
		0	18	19	15/10 ^a	300 MG/KG/DAY ^b
NUMBER OF GRAVID FEMALES		20	18	19	16	19
NUMBER OF CORPORA LUTEA	MEAN	8.3	9.1	8.9	9.0 ^c	8.5
	S.D.	2.0	1.9	2.3	2.1	1.9
NUMBER OF IMPLANTATIONS	MEAN	7.6	8.6	8.3	8.3	8.2
	S.D.	1.7	3.0	1.8	1.9	1.7
PERCENT PRE-IMPLANTATION LOSS	MEAN	7.9	9.0	5.6	6.7 ^c	4.4 ^d
	S.D.	12.8	24.3	9.3	10.2	9.3
NUMBER OF VIABLE FETUSES	MEAN	6.9	8.1 [*]	7.8	7.3	5.2
	S.D.	1.7	2.7	1.7	2.5	3.5
NUMBER OF NONVIABLE FETUSES	MEAN	0.0	0.0	0.0	0.1	0.0
	S.D.	0.0	0.0	0.0	0.3	0.0
NUMBER OF EARLY RESORPTIONS	MEAN	0.6	0.4	0.2	0.9	2.9 [*]
	S.D.	1.1	0.7	0.5	1.7	2.3
NUMBER OF LATE RESORPTIONS	MEAN	0.1	0.1	0.3	0.0	0.1
	S.D.	0.3	0.2	0.7	0.0	0.2
PERCENT POST-IMPLANTATION LOSS	MEAN	8.8	4.7	5.2	12.3	40.7 [*]
	S.D.	13.3	6.6	8.8	22.7	36.3
PERCENT TOTAL LOSS/LITTER	MEAN	16.1	13.7	10.8	15.4 ^c	44.3 ^{d*}
	S.D.	16.8	23.4	10.1	19.7	37.3

^a DUE TO MORTALITY, THE HIGH DOSE WAS REDUCED FROM 15 MG BASE/KG/DAY TO 10 MG BASE/KG/DAY ON GESTATION DAYS 12-15 (THE RANGE OF DAYS REFLECTS STUDY STAGGER-START OVER 4 DAYS).

^b RETINOL PALMITATE (75,000 I.U./KG/DAY ON GESTATION DAYS 9 AND 10, OR 9 AND 12 FOR 5 OF 20 ANIMALS - STUDY DEVIATION).

^c DOES NOT INCLUDE ONE FEMALE FOR WHICH CORPORA LUTEA WERE NOT RECORDED.

^d DOES NOT INCLUDE ONE FEMALE FOR WHICH IMPLANT COUNT EXCEEDED CORPORA LUTEA COUNT.
SIGNIFICANTLY DIFFERENT FROM CONTROL: * = $P < 0.05$

TABLE 3 (CONT.)

UIC/TRL STUDY NO.: 173 DEVELOPMENTAL TOXICITY (SEGMENT II) STUDY OF WR6026 DIHYDROCHLORIDE IN RABBITS
SUMMARY OF CESAREAN SECTION DATA

GROUP:		1		2		3		4		5	
DOSE LEVEL (MG BASE/KG/DAY):		0		3		7		15/10 ^a		300 MG/KG/DAY ^b	
SEX: MALES / FEMALES		3.8 3.1	3.8 4.2	3.8 4.2	3.6 4.3	3.6 4.3	4.0 3.3	2.8 3.4			
		2.0 1.3	1.8 1.8	2.0 1.7	2.0 1.7	2.0 1.7	1.9 2.1	1.8 2.2			
FETAL WEIGHT (g) (LITTER) ^c	MEAN	38.44	37.22	35.65	36.78	38.94					
	S.D.	4.90	5.91	4.62	4.18	4.35					
(MALES) ^c	MEAN	38.28	36.97	35.76	37.27	39.51					
	S.D.	4.92	5.08	5.19	5.18	5.33					
(FEMALES) ^c	MEAN	38.93	36.42	35.44	37.14	38.66					
	S.D.	5.58	6.22	4.82	4.06	4.40					
GRAVID UTERUS WEIGHT (g)	MEAN	365.22	399.64	394.36	384.00	294.20					
	S.D.	78.74	121.10	86.08	118.11	174.71					

^a DUE TO MORTALITY, THE HIGH DOSE WAS REDUCED FROM 15 MG BASE/KG/DAY TO 10 MG BASE/KG/DAY ON GESTATION DAYS 12-15. (THE RANGE OF DAYS REFLECTS STUDY STAGGER-START OVER 4 DAYS).

^b RETINOL PALMITATE (75,000 I.U./KG/DAY ON GESTATION DAYS 9 AND 10, OR 9 AND 12 FOR 5 OF 20 ANIMALS - STUDY DEVIATION).

^c VALUE FOR EACH GROUP REPRESENTS THE MEAN OF THE TOTAL OF THE LITTER MEANS.

SIGNIFICANTLY DIFFERENT FROM CONTROL: * = $P \leq 0.05$

TABLE 4

UIC/TRL STUDY NO.: 173 - DEVELOPMENTAL TOXICITY (SEGMENT II) STUDY OF WR6026 DIHYDROCHLORIDE IN RABBITS

SUMMARY OF FETAL OBSERVATIONS - MALFORMATIONS

- ABSOLUTE -

GROUP:	FETUSES			LITTERS			MG/KG/DAY ^b			MG/KG/DAY ^b		
	1	2	3	4	5	6	7	8	9	10	11	12
DOSE LEVEL (MG BASE/KG/DAY):	0	3	7	15/10 ^a	300	MG/KG/DAY ^b	0	0	0	0	0	0
NUMBER EXAMINED EXTERNALLY	137	145	149	117	99	20	18	19	16	16	5	5
MICROCEPHALY	0	0	0	0	9	0	0	0	0	0	3	3
CLEFT PALATE	0	0	0	0	6	0	0	0	0	0	5*	5*
MACROSTOMIA	0	0	0	0	13	0	0	0	0	0	4*	4*
FLESHY PROTUBERANCE/FACIAL BLEB(S)	1	0	0	0	34	1	0	0	0	0	11*	11*
MANDIBLE - MICROGNATHIA	0	0	0	0	1	0	0	0	0	0	1	1
MAXILLAE - MICROGNATHIA	0	0	0	0	3	0	0	0	0	0	3	3
PINNA ANOMALY	0	0	0	0	24	0	0	0	0	0	10*	10*
TAIL ANOMALY	0	0	1	1	30	0	0	1	1	1	10*	10*
ANAL ATRESIA	0	0	0	0	4	0	0	0	0	0	4*	4*
SMALL ANAL OPENING	0	0	0	0	1	0	0	0	0	0	1	1
TONGUE/MANDIBLE ANOMALY	0	0	0	0	2	0	0	0	0	0	1	1
MACROGLOSSIA	0	0	0	0	3	0	0	0	0	0	1	1
SMALL GENITAL TUBULE	0	0	0	0	1	0	0	0	0	0	1	1
MACROPHthalmia	0	1	0	0	0	0	1	0	0	0	0	0
NUMBER EXAMINED VISCERALLY	137	145	149	117	99	20	18	19	16	16	5*	5*
HEART AND/OR GREAT VESSEL ANOMALY	0	1	0	1	5	0	1	0	1	1	8*	8*
KIDNEY AND/OR URETER ANOMALY	1	0	0	3	13	1	0	0	1	1	0	0
DIAPHRAGMATIC HERNIA	0	0	0	1	0	0	0	0	1	1	0	0
HYDROCEPHALY	0	0	0	1	0	0	0	0	1	1	0	0
ANOPHTHALMIA/MICROPHthalmia	0	0	0	1	0	0	0	0	1	1	0	0

* DUE TO MORTALITY, THE HIGH DOSE WAS REDUCED FROM 15 MG BASE/KG/DAY TO 10 MG BASE/KG/DAY ON GESTATION DAYS 12-15 (THE RANGE OF DAYS REFLECTS STUDY STAGGER-START OVER 4 DAYS).

^b RETINOL PALMITATE (75,000 I.U./KG/DAY ON GESTATION DAYS 9 AND 10, OR 9 AND 12 FOR 5 OF 20 ANIMALS - STUDY DEVIATION).

NOTE: FOR DATA TABULATION PURPOSES, FINDINGS OF CLEFT PALATE OBSERVED AT SKELETAL EXAMINATION ARE COMBINED WITH THOSE OBSERVED AT THE EXTERNAL EXAMINATION

SIGNIFICANTLY DIFFERENT FROM CONTROL: * = P<0.05.

TABLE 4 (CONT.)

SUMMARY OF FETAL OBSERVATIONS - MALFORMATIONS

- ABSOLUTE -

GROUP: DOSE LEVEL (MG BASE/KG/DAY):	FETUSES			LITTERS			MG/KG/DAY ^b		
	1	2	3	4	5		15/10 ^a	300	5
NUMBER EXAMINED SKELETALLY	137	145	149	117	99	20	18	19	16
VERTEBRAL ANOMALY WITH ASSOCIATED RIB ANOMALY	0	1	1	7	0	0	1	1	0
VERTEBRAE ANOMALY	0	0	0	2	3	0	0	0	2
SKULL ANOMALY	0	0	1	0	67	0	0	1	14*
CAUDAL VERTEBRAE ANOMALY	0	0	0	0	8	0	0	0	6*
FUSED STERNEBRAE	3	1	0	2	1	2	1	0	1
8 CERVICAL VERTEBRAE	0	0	0	4	0	0	0	2	0
HYOID ANOMALY	0	0	0	0	60	0	0	0	15*
STERNEBRA (E) MALALIGNED - SEVERE	0	0	0	1	0	0	0	0	2
STERNEBRA (E) MALALIGNED AND FUSED	0	0	0	1	2	0	0	0	2
TOTAL MALFORMATIONS	1	1	1	1	60	1	1	1	15*
NUMBER WITH EXTERNAL MALFORMATIONS	1	1	0	3	16	1	1	0	10*
NUMBER WITH VISCERAL MALFORMATIONS	3	2	2	13	84	2	2	2	16*
TOTAL WITH MALFORMATIONS	5	4	3	13	87	3	4	3	16*

^a DUE TO MORTALITY, THE HIGH DOSE WAS REDUCED FROM 15 MG BASE/KG/DAY TO 10 MG BASE/KG/DAY ON GESTATION DAYS 12-15 (THE RANGE OF DAYS REFLECTS STUDY STAGGER-START OVER 4 DAYS).

^b RETINOL PALMITATE (75,000 I.U./KG/DAY ON GESTATION DAYS 9 AND 10, OR 9 AND 12 FOR 5 OF 20 ANIMALS - STUDY DEVIATION).

SIGNIFICANTLY DIFFERENT FROM CONTROL: * = $P \leq 0.05$.

UIC/TRL STUDY NO.: 173 DEVELOPMENTAL TOXICITY (SEGMENT II) STUDY OF WR6026 DIHYDROCHLORIDE IN RABBITS

SUMMARY OF FETAL OBSERVATIONS - VARIATIONS

GROUP:	FETUSES			LITTERS					
	1	2	3	3	4	5	1	2	3
DOSE LEVEL (MG BASE/KG/DAY):	0	3	7	15/10 ^a	300	MG/KG/DAY ^b	15/10 ^a	300	MG/KG/DAY ^b
NUMBER EXAMINED EXTERNALLY	137	145	149	117	99		20	18	19
NO EXTERNAL VARIATIONS OBSERVED									
NUMBER EXAMINED VISCERALLY	137	145	149	117	99		20	18	19
MAJOR BLOOD VESSEL VARIATION	14	6	13	21	15		5	4	5
THYROID VARIATION	0	0	2	0	2		0	0	1
GALL BLADDER VARIATION	0	0	1	6	9		0	0	1
SPLEEN - SMALL IN SIZE	0	0	1	1	0		0	0	1
HYDRONEPHROSIS	2	0	0	5	1		2	0	0
RETROCAVAL URETER	3	2	1	3	7		2	1	1
IRIS - HEMORRHAGIC RING	0	1	1	0	0		0	1	1
DISTENDED URETER	1	0	0	0	1		1	0	0

*DUE TO MORTALITY, THE HIGH DOSE WAS DECREASED FROM 15 MG BASE/KG/DAY TO 10 MG BASE/KG/DAY ON GESTATION DAYS 12-15 (THE RANGE OF DAYS REFLECTS STUDY STAGGER START OVER 4 DAYS).

RETINOL PALMITATE (75,000 I.U./KG/DAY ON GESTATION DAYS 9 AND 10, OR 9 AND 12 FOR 5 OF 20 ANIMALS - STUDY DEVIATION). SIGNIFICANTLY DIFFERENT FROM CONTROL: * = $P < 0.05$.

TABLE 5 (CONT.)

SUMMARY OF FETAL OBSERVATIONS - VARIATIONS

- ABSOLUTE -

GROUP: DOSE LEVEL (MG BASE/KG/DAY):	FETUSES			LITTERS			MG/KG/DAY ^b		
	1	2	3	4	5		15/10*	300	MG/KG/DAY ^b
NUMBER EXAMINED SKELETALLY	137	145	149	117	99	20	18	19	16
7TH STERNEBRA PRESENT	0	0	0	1	0	0	0	0	0
HYOID BODY UNOSSIFIED	1	4	4	1	0	1	3	4	1
HYOID ARCH(ES) UNOSSIFIED	1	1	0	0	0	1	1	0	0
STERNEBRA VARIATION	0	0	0	2	0	0	0	0	0
STERNEBRA(E) #1-#4 UNOSSIFIED	0	0	0	1	0	0	0	0	0
7TH CERVICAL RIBS	7	2	1	1	8	4	2	1	1
13TH FULL RIBS	52	67	75	45	37	19	16	19	13
13TH RUDIMENTARY RIBS	26	22	28	12	9	16	13	13	7
HYOID ARCH(ES) BENT	2	4	3	9	5	2	3	3	4
STERNEBRA(E) #5 - #6 UNOSSIFIED	13	47	27	20	15	6	14*	8	8
STERNEBRA(E) MALALIGNED (SLIGHT-MODERATE)	15	13	12	20	24	10	8	10	13
25 PRESACRAL VERTEBRAE	0	0	0	0	1	0	0	0	1
27 PRESACRAL VERTEBRAE	22	33	40	17	35	11	11	14	9
TALUS UNOSSIFIED	2	3	1	1	2	2	2	1	2
CALCANEUS UNOSSIFIED	0	0	0	0	1	0	0	0	1
TOTAL FETUSES/LITTERS WITH VARIATIONS	104	126	124	92	76	20	18	19	16

* DUE TO MORTALITY, THE HIGH DOSE WAS REDUCED FROM 15 MG BASE/KG/DAY TO 10 MG BASE/KG/DAY ON GESTATION DAYS 12-15 (THE RANGE OF DAYS REFLECTS STUDY STAGGER-START OVER 4 DAYS).

^b RETINOL PALMITATE (75,000 I.U./KG/DAY ON GESTATION DAYS 9 AND 10, OR 9 AND 12 FOR 5 OF 20 ANIMALS - STUDY DEVIATION).
SIGNIFICANTLY DIFFERENT FROM CONTROL: * = $P \leq 0.05$.

SUMMARY OF FETAL OBSERVATIONS - MALFORMATIONS

* DUE TO MORTALITY, THE HIGH DOSE WAS REDUCED FROM 15 MG BASE/KG/DAY TO 10 MG BASE/KG/DAY ON GESTATION DAYS 12-15 (THE RANGE OF DAYS REFLECTS STUDY STAGGER-START OVER 4 DAYS).

RETINOL PALMITATE (75,000 I.U./KG/DAY ON GESTATION DAYS 9 AND 10, OR 9 AND 12 FOR 5 OF 20 ANIMALS - STUDY DEVIATION).

NOTE: FOR DATA TABULATION PURPOSES, FINDINGS OF CLEFT PALATE OBSERVED AT SKELETAL EXAMINATION ARE COMBINED WITH THOSE OBSERVED AT THE EXTERNAL EXAMINATION

TABLE 6 (CONT.)

SUMMARY OF FETAL OBSERVATIONS - MALFORMATIONS

- PERCENT -

GROUP: DOSE LEVEL (MG BASE/KG/DAY):	FETUSES			LITTERS					
	1	2	3	4	5	1	2	3	4
	0	3	7	15/10*	300 MG/KG/DAY*	0	0	7	15/10*
NUMBER EXAMINED SKELETALLY	137	145	149	117	99	20	18	19	16
VERTEBRAL ANOMALY WITH ASSOCIATED RIB ANOMALY	0.0	0.7	0.7	6.0	0.0	0.0	5.6	5.3	12.5
VERTEBRAE ANOMALY	0.0	0.0	0.0	1.7	3.0	0.0	0.0	0.0	6.3
SKULL ANOMALY	0.0	0.0	0.7	0.0	67.7	0.0	0.0	5.3	0.0
CAUDAL VERTEBRAE ANOMALY	0.0	0.0	0.0	0.0	8.1	0.0	0.0	0.0	0.0
FUSED STERNEBRAE	2.2	0.7	0.0	1.7	1.0	10.0	5.6	0.0	12.5
8 CERVICAL VERTEBRAE	0.0	0.0	0.0	3.4	0.0	0.0	0.0	0.0	12.5
HYOID ANOMALY	0.0	0.0	0.0	0.0	60.6	0.0	0.0	0.0	0.0
STERNEBRA (E) MALALIGNED - SEVERE	0.0	0.0	0.0	0.9	0.0	0.0	0.0	0.0	0.0
STERNEBRA (E) MALALIGNED AND FUSED	0.0	0.0	0.0	0.9	2.0	0.0	0.0	0.0	6.3
TOTAL MALFORMATIONS									
NUMBER WITH EXTERNAL MALFORMATIONS	0.7	0.7	0.7	0.9	60.6	5.0	5.6	5.3	6.3
NUMBER WITH VISCERAL MALFORMATIONS	0.7	0.7	0.0	2.6	16.2	5.0	5.6	0.0	6.3
NUMBER WITH SKELETAL MALFORMATIONS	2.2	1.4	1.3	11.1	84.8	10.0	11.1	10.5	25.0
TOTAL WITH MALFORMATIONS	3.6	2.8	2.0	11.1	87.9	15.0	22.2	15.8	25.0

* DUE TO MORTALITY, THE HIGH DOSE WAS REDUCED FROM 15 MG BASE/KG/DAY TO 10 MG BASE/KG/DAY ON GESTATION DAYS 12-15 (THE RANGE OF DAYS REFLECTS STUDY STAGGER-START OVER 4 DAYS).

^b RETINOL PALMITATE (75,000 I.U./KG/DAY ON GESTATION DAYS 9 AND 10, OR 9 AND 12 FOR 5 OF 20 ANIMALS - STUDY DEVIATION).

UIC/TRL STUDY NO.: 173 DEVELOPMENTAL TOXICITY (SEGMENT II) STUDY OF WR6026 DIHYDROCHLORIDE IN RABBITS
SUMMARY OF FETAL OBSERVATIONS - VARIATIONS

TABLE 7

- PERCENT -

GROUP: DOSE LEVEL (MG BASE/KG/DAY):	FETUSES			LITTERS		
	1	2	3	1	2	3
	0	0	3	0	0	0
	137	145	149	117	99	16
NUMBER EXAMINED EXTERNALLY	137	145	149	117	99	16
NO EXTERNAL VARIATIONS OBSERVED						
NUMBER EXAMINED VISCERALLY	137	145	149	117	99	16
MAJOR BLOOD VESSEL VARIATION	10.2	4.1	8.7	17.9	15.2	68.8
THYROID VARIATION	0.0	0.0	1.3	0.0	2.0	0.0
GALL BLADDER VARIATION	0.0	0.0	0.7	5.1	9.1	12.5
SPLEEN - SMALL IN SIZE	0.0	0.0	0.7	0.9	0.0	0.0
HYDRONEPHROSIS	1.5	0.0	0.0	4.3	1.0	6.3
RETROCAVAL URETER	2.2	1.4	0.7	2.6	7.1	37.5
IRIS - HEMORRHAGIC RING	0.0	0.7	0.7	0.0	0.0	0.0
DISTENDED URETER	0.7	0.0	0.0	0.0	1.0	6.3

*DUE TO MORTALITY, THE HIGH DOSE WAS DECREASED FROM 15 MG BASE/KG/DAY TO 10 MG BASE/KG/DAY ON GESTATION DAYS 12-15 (THE RANGE OF DAYS REFLECTS STUDY STAGGER START OVER 4 DAYS).

^bRETINOL PALMITATE (75,000 I.U./KG/DAY ON GESTATION DAYS 9 AND 10, OR 9 AND 12 FOR 5 OF 20 ANIMALS - STUDY DEVIATION).

TABLE 7 (CONT.)

UIC/TRL STUDY NO.: 173 DEVELOPMENTAL TOXICITY (SEGMENT II) STUDY OF WR6026 DIHYDROCHLORIDE IN RABBITS
SUMMARY OF FETAL OBSERVATIONS - VARIATIONS

NUMBER EXAMINED SKELETALLY	- PERCENT -									
	FETUSES					LITTERS				
	1	2	3	4	5	1	2	3	4	5
GROUP: DOSE LEVEL (MG BASE/KG/DAY):	0	3	7	15/10 ^a	300 MG/KG/DAY ^b	0	3	7	15/10 ^a	300 MG/KG/DAY ^b
7TH STERNEBRA PRESENT	137	145	149	117	99	20	18	19	16	16
HYOID BODY UNOSSIFIED	0.0	0.0	0.0	0.9	0.0	0.0	0.0	0.0	6.3	0.0
HYOID ARCH(ES) UNOSSIFIED	0.7	2.8	2.7	0.9	0.0	5.0	16.7	21.1	6.3	0.0
STERNEBRA VARIATION	0.0	0.0	0.0	0.0	0.0	5.0	5.6	0.0	0.0	0.0
STERNEBRA(E) #1-#4 UNOSSIFIED	0.0	0.0	0.0	1.7	0.0	0.0	0.0	0.0	6.3	0.0
7TH CERVICAL RIBS	5.1	1.4	0.7	0.9	8.1	0.0	0.0	0.0	6.3	0.0
13TH FULL RIBS	38.0	46.9	50.3	38.5	37.4	20.0	11.1	5.3	6.3	31.3
13TH RUDIMENTARY RIBS	19.0	15.1	18.8	10.3	9.1	95.0	88.9	100.0	81.3	81.3
HYOID ARCH(ES) BENT	1.5	2.8	2.0	7.7	5.1	80.0	72.2	68.4	56.3	43.8
STERNEBRA(E) #5 - #6 UNOSSIFIED	9.5	32.4	18.1	17.1	15.2	10.0	16.7	15.8	50.0	25.0
STERNEBRA(E) MALALIGNED						30.0	77.8	42.1	56.3	50.0
(SLIGHT-MODERATE)	10.9	9.0	8.1	16.4	24.2	50.0	44.4	52.6	81.3	81.3
25 PRESACRAL VERTEBRAE	0.0	0.0	0.0	0.0	1.0	0.0	0.0	0.0	0.0	6.3
27 PRESACRAL VERTEBRAE	16.1	22.8	26.8	14.5	35.4	55.0	61.1	73.7	56.3	75.0
TALUS UNOSSIFIED	1.5	2.1	0.7	0.9	2.0	10.0	11.1	5.3	6.3	12.5
CALCANEUS UNOSSIFIED	0.0	0.0	0.0	0.0	1.0	0.0	0.0	0.0	0.0	6.3
TOTAL FETUSES/LITTERS WITH VARIATIONS	75.9	86.9	83.2	78.6	76.8	100.0	100.0	100.0	100.0	100.0

^a DUE TO MORTALITY, THE HIGH DOSE WAS REDUCED FROM 15 MG BASE/KG/DAY TO 10 MG BASE/KG/DAY ON GESTATION DAYS 12-15 (THE RANGE OF DAYS REFLECTS STUDY STAGGER-START OVER 4 DAYS).

^b RETINOL PALMITATE (75,000 I.U./KG/DAY ON GESTATION DAYS 9 AND 10, OR 9 AND 12 FOR 5 OF 20 ANIMALS - STUDY DEVIATION).

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APPENDIX A

UIC/TRL STUDY NO.: 173 DEVELOPMENTAL TOXICITY (SEGMENT II) STUDY OF WR6026 DIHYDROCHLORIDE IN RABBITS

INDIVIDUAL MATERNAL GROSS NECROPSY OBSERVATIONS

GROUP 1: 0 MG BASE/KG/DAY

DAM#	ORGAN	OBSERVATION
701		NO ABNORMALITIES DETECTED
702		NO ABNORMALITIES DETECTED
703		NO ABNORMALITIES DETECTED
704		NO ABNORMALITIES DETECTED
705		NO ABNORMALITIES DETECTED
706		NO ABNORMALITIES DETECTED
707		NO ABNORMALITIES DETECTED
708		NO ABNORMALITIES DETECTED
709		NO ABNORMALITIES DETECTED
710		NO ABNORMALITIES DETECTED
711		NO ABNORMALITIES DETECTED
712		NO ABNORMALITIES DETECTED
713		NO ABNORMALITIES DETECTED
714		NO ABNORMALITIES DETECTED
715		NO ABNORMALITIES DETECTED
716		NO ABNORMALITIES DETECTED
717		NO ABNORMALITIES DETECTED
718		NO ABNORMALITIES DETECTED
719		NO ABNORMALITIES DETECTED
720		NO ABNORMALITIES DETECTED

DEVELOPMENTAL TOXICITY (SEGMENT II) STUDY OF WR6026 DIHYDROCHLORIDE IN RABBITS

INDIVIDUAL MATERNAL GROSS NECROPSY OBSERVATIONS

GROUP 2: 3 MG BASE/KG/DAY

DAM#	ORGAN	OBSERVATION
721		NO ABNORMALITIES DETECTED
722		NO ABNORMALITIES DETECTED
723		NO ABNORMALITIES DETECTED
724		NO ABNORMALITIES DETECTED
725		NO ABNORMALITIES DETECTED
726		NO ABNORMALITIES DETECTED
727		NO ABNORMALITIES DETECTED
728		NO ABNORMALITIES DETECTED
		NONGRAVID - AMMONIUM SULFIDE TEST NEGATIVE
729		NO ABNORMALITIES DETECTED
730		NO ABNORMALITIES DETECTED
731		NO ABNORMALITIES DETECTED
732		NO ABNORMALITIES DETECTED
733		NO ABNORMALITIES DETECTED
734		NO ABNORMALITIES DETECTED
735		NO ABNORMALITIES DETECTED
736		NO ABNORMALITIES DETECTED
737		NO ABNORMALITIES DETECTED
738		NO ABNORMALITIES DETECTED
739		NO ABNORMALITIES DETECTED
740		CYST
	LEFT OVIDUCT	
		NONGRAVID - AMMONIUM SULFIDE TEST NEGATIVE

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APPENDIX A

UIC/TRL STUDY NO.: 173 DEVELOPMENTAL TOXICITY (SEGMENT II) STUDY OF WR6026 DIHYDROCHLORIDE IN RABBITS
INDIVIDUAL MATERNAL GROSS NECROPSY OBSERVATIONS

GROUP 3: 7 MG BASE/KG/DAY

DAM#	ORGAN	OBSERVATION
741		NO ABNORMALITIES DETECTED
742		NO ABNORMALITIES DETECTED
743		NO ABNORMALITIES DETECTED
744		NO ABNORMALITIES DETECTED
745		NO ABNORMALITIES DETECTED
746		NO ABNORMALITIES DETECTED
747		NO ABNORMALITIES DETECTED
748		NO ABNORMALITIES DETECTED
749		NO ABNORMALITIES DETECTED
750		NO ABNORMALITIES DETECTED
751		NO ABNORMALITIES DETECTED
752		NO ABNORMALITIES DETECTED
753		NO ABNORMALITIES DETECTED
754		NO ABNORMALITIES DETECTED
755		NO ABNORMALITIES DETECTED
756		NO ABNORMALITIES DETECTED
		SACRIFICED MORIBUND - GESTATION DAY 8
		BLOOD ON BACK OF ABDOMINAL WALL, POSSIBLY DUE TO PRIOR BACK INJURY; CORPORA LUTEA: 4, LEFT;
		5, RIGHT; UTERINE IMPLANTATIONS: 4 NONVIABLE FETUSES, LEFT; 2 NONVIABLE FETUSES AND 2 EARLY
		RESORPTIONS, RIGHT
757		NO ABNORMALITIES DETECTED
758		NO ABNORMALITIES DETECTED
759		NO ABNORMALITIES DETECTED
760		NO ABNORMALITIES DETECTED

APPENDIX A

UIC/TRL STUDY NO.: 173 DEVELOPMENTAL TOXICITY (SEGMENT II) STUDY OF WR6026 DIHYDROCHLORIDE IN RABBITS

INDIVIDUAL MATERNAL GROSS NECROPSY OBSERVATIONS

GROUP 4: 15/10 MG BASE/KG/DAY*

DAM#	ORGAN	OBSERVATION
761		NO ABNORMALITIES DETECTED
762		NO ABNORMALITIES DETECTED
763		FOUND DEAD - GESTATION DAY 14
		NO ABNORMALITIES DETECTED; CORPORA LUTEA: 4, LEFT; 6, RIGHT; UTERINE IMPLANTATIONS: 5 LATE RESORPTIONS, LEFT; 5 LATE RESORPTIONS, RIGHT
764	RECTUM	FOUND DEAD - GESTATION DAY 8
		MASSIVE SOAKING WITH URINE AND STOOL; CORPORA LUTEA: 4, LEFT; NOT RECORDED, RIGHT; UTERINE IMPLANTATIONS: 3 LATE RESORPTIONS, LEFT; 5 LATE RESORPTIONS, RIGHT
765	VAGINA	FOUND DEAD - GESTATION DAY 10
		BROWN THICK SECRETION AROUND THE OPENING AND INSIDE THE CANAL; CORPORA LUTEA: 6, LEFT; 4, RIGHT; UTERINE IMPLANTATIONS: 5 LATE RESORPTIONS, LEFT; 5 LATE RESORPTIONS, RIGHT
766		NO ABNORMALITIES DETECTED
767		NO ABNORMALITIES DETECTED
768		NO ABNORMALITIES DETECTED
769		NO ABNORMALITIES DETECTED
770		NO ABNORMALITIES DETECTED
771		NO ABNORMALITIES DETECTED
772		NO ABNORMALITIES DETECTED
773		NO ABNORMALITIES DETECTED
774		NO ABNORMALITIES DETECTED
775	STOMACH	FOUND DEAD - GESTATION DAY 11
		RUPTURED WITH MATERIAL IN ABDOMINAL CAVITY; CORPORA LUTEA: 8, LEFT; 2, RIGHT; UTERINE IMPLANTATIONS: 8 LATE RESORPTIONS, LEFT; 2 LATE RESORPTIONS, RIGHT
776		NO ABNORMALITIES DETECTED
777		NO ABNORMALITIES DETECTED
778		NO ABNORMALITIES DETECTED
779		NO ABNORMALITIES DETECTED
780		NO ABNORMALITIES DETECTED

* DUE TO MORTALITY, THE HIGH DOSE WAS REDUCED FROM 15 MG BASE/KG/DAY TO 10 MG BASE/KG/DAY ON GESTATION DAYS 12-15 (THE RANGE OF DAYS REFLECTS STUDY STAGGER-START OVER 4 DAYS).

UIC/TRL

UIC/TRL STUDY NO.: 173 DEVELOPMENTAL TOXICITY (SEGMENT II) STUDY OF WR6026 DIHYDROCHLORIDE IN RABBITS
 APPENDIX A
 INDIVIDUAL MATERNAL GROSS NECROPSY OBSERVATIONS

GROUP 5: 300 MG/KG/DAY (RETINOL PALMITATE)

DAM#	ORGAN	OBSERVATION
781		NO ABNORMALITIES DETECTED
782		NO ABNORMALITIES DETECTED
783		NO ABNORMALITIES DETECTED
784		NO ABNORMALITIES DETECTED
785		NO ABNORMALITIES DETECTED
786		NO ABNORMALITIES DETECTED
787		NO ABNORMALITIES DETECTED
788		NO ABNORMALITIES DETECTED
789		NO ABNORMALITIES DETECTED
790		NO ABNORMALITIES DETECTED
		NONGRAVID - AMMONIUM SULFIDE TEST NEGATIVE
791		NO ABNORMALITIES DETECTED
792		NO ABNORMALITIES DETECTED
793		NO ABNORMALITIES DETECTED
794		NO ABNORMALITIES DETECTED
795		NO ABNORMALITIES DETECTED
796		NO ABNORMALITIES DETECTED
797		NO ABNORMALITIES DETECTED
798		NO ABNORMALITIES DETECTED
799		NO ABNORMALITIES DETECTED
800		NO ABNORMALITIES DETECTED

UIC/TRL STUDY NO.: 173

APPENDIX B

DEVELOPMENTAL TOXICITY (SEGMENT II) STUDY OF WR6026 DIHYDROCHLORIDE IN RABBITS
INDIVIDUAL CESAREAN SECTION DATA

GROUP 1: 0 MG BASE/KG/DAY

DAM#	CORPORA LUTEA		IMPLANTATIONS		SEX		VIABLE FETUSES		NONVIABLE FETUSES		EARLY RESORPTIONS		LATE RESORPTIONS	
	LEFT RIGHT TOTAL		LEFT RIGHT TOTAL		M F		LEFT RIGHT TOTAL		LEFT RIGHT TOTAL		LEFT RIGHT TOTAL		LEFT RIGHT TOTAL	
	LEFT	RIGHT	LEFT	RIGHT	M	F	LEFT	RIGHT	LEFT	RIGHT	LEFT	RIGHT	LEFT	RIGHT
701	6	6	12	5	7	1	4	4	0	0	0	0	0	1
702	3	5	8	4	1	4	1	4	0	0	0	0	0	0
703	3	7	10	7	7	3	3	7	0	0	0	0	0	0
704	3	4	7	4	3	4	3	4	0	0	0	0	0	0
705	4	4	8	4	4	3	4	3	0	0	0	0	0	1
706	6	7	13	7	5	3	1	7	0	0	0	0	0	0
707	3	6	9	6	3	5	2	6	0	0	0	0	0	0
708	4	4	8	4	5	2	4	3	0	0	1	1	0	0
709	3	5	8	5	5	3	3	5	0	0	0	0	0	0
710	7	2	9	2	7	2	7	2	0	0	0	0	0	0
711	3	2	5	2	1	4	3	2	0	0	0	0	0	0
712	3	3	6	3	2	4	3	3	0	0	0	0	0	0
713	5	4	9	3	5	1	4	2	0	0	1	2	0	0
714	6	3	9	3	5	4	6	3	0	0	0	0	0	0
715	2	7	9	7	4	2	1	5	0	0	1	2	0	0
716	3	3	6	3	4	2	3	3	0	0	0	0	0	0
717	4	3	7	2	2	4	4	2	0	0	0	0	0	0
718	2	3	5	3	2	1	0	3	0	0	1	0	0	0
719	7	2	9	2	3	5	6	2	0	0	1	0	1	0
720	7	2	9	2	1	4	3	2	0	0	4	0	0	0
TOTAL	166	151	317	137	76	61	137	0	0	0	12	2	0	2
MEAN	8.3	7.6	15.9	6.9	3.8	3.1	6.9	0.0	0.0	0.0	0.6	0.1	0.1	0.1
S.D.	2.0	1.7	3.7	1.7	2.0	1.3	1.7	0.0	0.0	0.0	1.1	0.3	0.3	0.3
N	20	20	40	20	20	20	20	20	20	20	20	20	20	20

UIC/TRL STUDY NO.: 173 DEVELOPMENTAL TOXICITY (SEGMENT II) STUDY OF WR6026 DIHYDROCHLORIDE IN RABBITS

APPENDIX B

INDIVIDUAL CESAREAN SECTION DATA

GROUP 2: 3 MG BASE/KG/DAY

DAM#	CORPORA LUTEA		TOTAL IMPLANTATIONS		SEX		VIABLE FETUSES		NONVIABLE FETUSES		EARLY RESORPTIONS		LATE RESORPTIONS	
	LEFT RIGHT		LEFT RIGHT		M F		LEFT RIGHT		LEFT RIGHT		LEFT RIGHT		LEFT RIGHT	
	LEFT	RIGHT	LEFT	RIGHT	TOTAL	TOTAL	LEFT	RIGHT	LEFT	RIGHT	LEFT	RIGHT	LEFT	RIGHT
721	3	8	11	3	8	11	6	4	2	8	10	0	0	0
722	2	6	8	2	6	8	3	5	2	6	8	0	0	0
723	4	8	12	4	8	12	5	6	4	7	11	0	1	0
724	7	4	11	7	4	11	6	4	7	3	10	0	1	0
725	6	0	6	1	0	1	0	1	1	0	1	0	0	0
726	3	4	7	3	4	7	5	2	3	4	7	0	0	0
727	4	3	7	4	3	7	3	4	4	3	7	0	0	0
728	NONGRAVID													
729	4	7	11	4	7	11	3	8	4	7	11	0	0	0
730	5	4	9	5	4	9	4	4	4	4	8	0	1	0
731	5	4	9	5	4	9	3	6	5	4	9	0	0	0
732	4	7	11	4	7	11	3	6	3	6	9	0	1	0
733	6	5	11	6	5	11	7	4	6	5	11	0	0	0
734	3	3	6	1	1	2	1	1	1	1	2	0	0	0
735	5	6	11	5	6	11	4	5	4	5	9	0	1	0
736	2	6	8	2	6	8	5	3	2	6	8	0	0	0
737	5	4	9	4	4	8	5	3	4	4	8	0	0	0
738	7	2	9	7	2	9	2	6	6	2	8	0	0	1
739	6	2	8	6	2	8	4	4	6	2	8	0	0	0
740	NONGRAVID													
TOTAL	164	154	69	76	145	0	8	1	0	0	0	0	0	1
MEAN	9.1	8.6	3.8	4.2	8.1	0.0	0.4	0.1	0.0	0.0	0.0	0.0	0.0	0.1
S.D.	1.9	3.0	1.8	1.8	2.7	0.0	0.7	0.2	0.0	0.0	0.0	0.0	0.0	0.2
N	18	18	18	18	18	18	18	18	18	18	18	18	18	18

UIC/TRL STUDY NO.: 173 DEVELOPMENTAL TOXICITY (SEGMENT II) STUDY OF WR6026 DIHYDROCHLORIDE IN RABBITS
 APPENDIX B
 INDIVIDUAL CESAREAN SECTION DATA

GROUP 3: 7 MG BASE/KG/DAY

DAM#	TOTAL										EARLY RESORPTIONS				LATE RESORPTIONS			
	CORPORA LUTEA					IMPLANTATIONS					SEX		VIABLE FETUSES		NONVIABLE FETUSES		LEFT	
	LEFT	RIGHT	TOTAL	LEFT	RIGHT	TOTAL	M	F	LEFT	RIGHT	TOTAL	LEFT	RIGHT	TOTAL	LEFT	RIGHT	TOTAL	LEFT
741	4	8	12	3	7	10	6	4	3	7	10	0	0	0	0	0	0	0
742	3	5	8	3	5	8	4	3	3	4	7	0	0	0	0	0	1	1
743	5	8	13	4	6	10	6	4	4	6	10	0	0	0	0	0	0	0
744	6	3	9	6	3	9	5	4	6	3	9	0	0	0	0	0	0	0
745	6	7	13	6	6	12	5	7	6	6	12	0	0	0	0	0	0	0
746	5	2	7	5	2	7	6	1	5	2	7	0	0	0	0	0	0	0
747	1	7	8	1	6	7	4	3	1	6	7	0	0	0	0	0	0	0
748	5	6	11	3	5	8	3	5	3	5	8	0	0	0	0	0	0	0
749	5	4	9	5	4	9	4	5	5	4	9	0	0	0	0	0	0	0
750	4	6	10	3	7	10	0	7	2	5	7	0	0	0	0	0	1	2
751	4	4	8	4	4	8	2	5	4	3	7	0	0	0	1	0	0	0
752	7	2	9	7	2	9	3	5	6	2	8	0	0	0	0	0	1	0
753	4	3	7	4	3	7	2	5	4	3	7	0	0	0	0	0	0	0
754	8	2	10	6	2	8	7	1	6	2	8	0	0	0	0	0	0	0
755	3	5	8	3	5	8	1	6	2	5	7	0	0	0	1	0	0	0
756	SACRIFICED MORIBUND - GESTATION DAY 8																	
757	6	2	8	6	2	8	4	4	6	2	8	0	0	0	0	0	0	0
758	7	3	10	7	3	10	2	6	6	2	8	0	0	0	1	1	2	0
759	5	1	6	5	1	6	3	3	5	1	6	0	0	0	0	0	0	0
760	2	2	4	2	2	4	1	3	2	2	4	0	0	0	0	0	0	0
TOTAL	170			158	68	81					149	0	4				5	
MEAN	8.9			8.3	3.6	4.3					7.8	0.0	0.2				0.3	
S.D.	2.3			1.8	2.0	1.7					1.7	0.0	0.5				0.7	
N	19			19	19	19					19	19	19				19	

APPENDIX B

INDIVIDUAL CESAREAN SECTION DATA

GROUP 4: 15/10 MG BASE/KG/DAY*

DAM#	CORPORA LUTEA		TOTAL		IMPLANTATIONS		SEX		VIABLE FETUSES		NONVIABLE FETUSES		EARLY RESORPTIONS		LATE RESORPTIONS	
	LEFT RIGHT TOTAL		LEFT RIGHT TOTAL		LEFT RIGHT TOTAL		M F		LEFT RIGHT TOTAL		LEFT RIGHT TOTAL		LEFT RIGHT TOTAL		LEFT RIGHT TOTAL	
	5	7	12	5	7	12	4	6	4	6	0	0	1	1	2	0
761	5	7	12	5	7	12	4	6	4	6	0	0	1	1	2	0
762	5	6	11	5	6	11	7	4	5	6	0	0	0	0	0	0
763	FOUND DEAD - GESTATION DAY 14															
764	FOUND DEAD - GESTATION DAY 8															
765	FOUND DEAD - GESTATION DAY 10															
766	7	5	12	4	4	8	4	3	4	3	0	0	0	1	1	0
767	3	4	7	3	4	7	5	2	3	4	0	0	0	0	0	0
768	3	5	8	3	4	7	6	1	3	4	0	0	0	0	0	0
769	b	b	b	3	5	8	2	1	0	3	0	0	3	2	5	0
770	5	4	9	4	4	8	4	4	4	4	0	0	0	0	0	0
771	4	3	7	4	3	7	4	4	4	3	0	0	0	0	0	0
772	4	4	8	4	4	8	5	3	4	4	0	0	0	0	0	0
773	3	4	7	2	4	6	3	3	2	4	0	0	0	0	0	0
774	4	6	10	4	6	10	1	9	4	6	0	0	0	0	0	0
775	FOUND DEAD - GESTATION DAY 11															
776	5	8	13	4	8	12	8	3	4	7	0	1	0	0	0	0
777	4	3	7	4	3	7	2	0	1	1	0	0	3	2	5	0
778	4	5	9	3	4	7	4	3	3	4	0	0	0	0	0	0
779	4	3	7	4	3	7	3	4	4	3	0	0	0	0	0	0
780	2	6	8	2	6	8	2	4	1	5	0	0	1	1	2	0
TOTAL	135		133	64	53						1		15			0
MEAN	9.0		8.3	4.0	3.3						0.1		0.9			0.0
S.D.	2.1		1.9	1.9	2.1						0.3		1.7			0.0
N	15		16	16	16						16		16			16

* DUE TO MORTALITY, THE HIGH DOSE WAS REDUCED FROM 15 MG BASE/KG/DAY TO 10 MG BASE/KG/DAY ON GESTATION DAYS 12-15 (THE RANGE OF DAYS REFLECTS STUDY STAGGER-START OVER 4 DAYS).

b = CORPORA LUTEA NOT RECORDED, NOT INCLUDED IN CALCULATIONS.

APPENDIX B

INDIVIDUAL CESAREAN SECTION DATA

GROUP 5: 300 MG/KG/DAY (RETINOL PALMITATE)

DAM#	CORPORA LUTEA		TOTAL		IMPLANTATIONS		SEX		VIABLE FETUSES		NONVIABLE FETUSES		EARLY RESORPTIONS		LATE RESORPTIONS	
	LEFT RIGHT		LEFT RIGHT		LEFT RIGHT		M F		LEFT RIGHT		LEFT RIGHT		LEFT RIGHT		LEFT RIGHT	
	TOTAL		TOTAL		TOTAL		TOTAL		TOTAL		TOTAL		TOTAL		TOTAL	
781	7	6	13	7	6	3	13	1	10	6	5	11	0	0	1	1
782	6	6	12	6	3	7	9	1	4	4	1	5	0	0	2	2
783	2	7	9	2	7	3	9	5	3	1	7	8	0	0	1	0
784	1	8	9	1	8	9	9	5	4	1	8	9	0	0	0	1
785	5	3	8	5	4	4	9	4	4	5	3	8	0	0	0	0
786	5	2	7	4	2	4	6	0	1	0	1	1	0	0	1	1
787	3	5	8	3	5	3	8	3	5	3	5	8	0	0	4	1
788	4	3	7	4	3	7	7	-	-	0	0	0	0	0	0	0
789	4	6	10	4	3	7	7	2	1	2	1	3	0	0	2	2
790	NONGRAVID															
791	5	1	6	5	1	6	6	2	3	4	1	5	0	0	0	0
792	4	2	6	4	2	6	6	-	-	0	0	0	0	0	4	2
793	8	1	9	8	1	9	9	4	2	5	1	6	0	0	3	0
794	3	6	9	3	6	9	9	6	3	3	6	9	0	0	0	0
795	4	6	10	3	6	9	9	3	3	2	4	6	0	0	1	2
796	5	2	7	5	2	7	7	0	1	1	0	1	0	0	4	2
797	3	5	8	3	5	8	8	3	2	1	4	5	0	0	2	1
798	5	4	9	5	4	9	9	1	5	4	2	6	0	0	1	2
799	2	4	6	2	4	6	6	-	-	0	0	0	0	0	2	4
800	4	5	9	4	5	9	9	4	4	4	4	8	0	0	0	1
TOTAL	162		155	44	55	99							0		55	1
MEAN	8.5		8.2	2.8	3.4	5.2							0.0		2.9	0.1
S.D.	1.9		1.7	1.8	2.2	3.5							0.0		2.3	0.2
N	19		19	16	16	19							19		19	19

APPENDIX C

UIC/TRL STUDY NO.: 173

DEVELOPMENTAL TOXICITY (SEGMENT II) STUDY OF WR6026 DIHYDROCHLORIDE IN RABBITS

INDIVIDUAL GRAVID UTERUS AND FETAL BODY WEIGHT DATA (GRAMS)

GROUP 1: 0 MG BASE/KG/DAY

DAM #	GRAVID UTERUS WEIGHT	MEAN FETAL WEIGHT	INDIVIDUAL FETAL WEIGHT												
			1	2	3	4	5	6	7	8	9	10	11	12	13
701	457.00	37.85	44.12M	35.03M	31.91M	39.09M	41.25P	39.64M	L	37.27M	34.52M
702	319.72	46.31	49.23P	48.29P	45.95P	43.28M	44.79P
703	542.00	39.53	43.75M	40.82M	41.09M	42.99M	39.56P	40.90M	43.70M	40.70M	28.39P	33.35P	.	.	.
704	407.78	42.74	44.62F	41.25M	45.65M	42.53M	42.09P	41.55F	41.50P
705	413.13	37.79	42.89P	37.78M	35.98M	34.93F	42.78M	L	31.89P	38.24M
706	351.24	31.73	23.11F	38.01M	30.56M	31.19P	30.12M	35.70F	29.69M	35.45M
707	391.58	35.82	41.51M	34.02P	40.59M	36.01P	37.03P	33.97F	29.49M	33.90P
708	401.75	40.63	43.66M	38.14M	31.91M	40.40M	43.36P	43.57P	E	43.40M
709	407.20	37.90	41.31F	38.96M	33.56M	39.21F	41.12P	37.71M	33.69M	37.61M
710	429.32	33.74	36.32M	32.98F	31.38M	34.75M	33.40M	26.40M	33.18M	38.88M	36.33P
711	262.76	36.22	41.90F	36.13M	30.95P	38.22P	33.90P
712	297.83	35.98	38.06P	35.04P	32.20M	38.58M	35.54P	36.46P
713	282.83	33.17	30.91M	E	33.58M	29.32M	33.34M	E	35.71P	36.15M
714	462.58	35.46	37.78M	37.27M	37.93P	37.57M	29.42P	35.40M	34.71M	34.98P	34.05P
715	308.11	35.97	44.72P	E	E	38.89P	34.20M	33.25M	27.42M	37.35M
716	319.19	39.50	41.50P	37.43P	36.33M	46.87M	38.86M	36.02M
717	383.65	46.18	49.86F	40.72P	46.51M	44.03P	51.97M	43.96P
718	219.68	49.58	E	48.28M	52.57F	47.88M
719	356.46	31.55	38.75P	E	35.02M	22.41P	28.22M	24.47F	32.04M	36.78P	34.73P
720	290.62	41.26	41.28P	E	E	E	E	39.47M	40.97P	44.87P	39.70P

KEY: E= EARLY RESORPTION L= LATE RESORPTION

M=MALE F=FEMALE

APPENDIX C

UIC/TRL STUDY NO.: 173

DEVELOPMENTAL TOXICITY (SEGMENT II) STUDY OF WR6026 DIHYDROCHLORIDE IN RABBITS

INDIVIDUAL GRAVID UTERUS AND FETAL BODY WEIGHT DATA (GRAMS)

GROUP 2: 3 MG BASE/KG/DAY

DAM #	GRAVID UTERUS WEIGHT	MEAN FETAL WEIGHT	INDIVIDUAL FETAL WEIGHT											12	13
			1	2	3	4	5	6	7	8	9	10	11		
721	552.31	39.19	E	47.51F	44.56F	47.21M	40.50F	32.65F	32.84M	35.57M	33.65M	35.53M	41.88M	.	.
722	436.01	41.68	46.31F	37.64F	53.32M	45.43F	40.73F	35.49F	33.49M	41.04M
723	518.03	34.26	40.82M	31.90F	37.22M	36.53M	44.49F	E	36.95F	26.60F	30.44M	38.77F	29.59M	23.53F	.
724	367.83	26.44	35.40M	27.87F	28.45M	25.38M	21.04M	13.84F	20.38F	30.89M	30.37M	E	30.75F	.	.
725	80.15	52.37	52.37F
726	398.57	41.17	41.12M	36.59F	39.59M	46.37M	42.43F	37.76M	44.32M
727	336.09	34.20	40.18M	32.09M	29.61F	29.46F	37.37F	34.96F	35.70M
728	NONGRAVID														
729	490.77	33.68	44.25M	38.41F	30.27F	29.43F	39.37M	37.87F	37.18F	34.56F	28.07F	24.37F	26.72M	.	.
730	405.09	34.29	E	44.92M	33.78F	25.09F	31.81M	39.28M	31.94M	34.02F	33.51F
731	484.83	40.69	43.82F	39.33F	39.21F	36.78M	43.29F	46.14M	41.64F	39.75M	36.28F
732	423.45	32.49	35.21F	33.59F	29.44F	E	38.26M	34.05F	37.99F	E	26.71M	25.90F	31.26M	.	.
733	487.89	33.39	35.40F	36.43M	35.68M	29.34F	34.85M	35.54F	39.09M	37.29M	33.70M	28.51F	21.51M	.	.
734	130.22	41.71	38.78F	44.63M
735	358.72	28.44	33.95M	31.87F	28.09M	E	28.85M	E	32.24F	32.85F	29.57F	24.16F	14.34M	.	.
736	428.22	39.22	47.86M	40.85M	43.32M	41.24F	39.48M	34.25F	32.17M	34.60F
737	461.80	41.26	46.45M	42.55M	34.71F	38.20M	42.50F	43.66F	41.70M	40.32M
738	421.47	36.94	44.29F	41.38F	36.86M	34.28F	27.91F	28.97M	L	44.97F	36.85F
739	412.10	38.59	39.90M	39.47M	32.19F	34.78M	36.50F	41.39F	43.71M	40.79F
740	NONGRAVID														

KEY: E= EARLY RESORPTION L= LATE RESORPTION

M=MALE F=FEMALE

UIC/TRL STUDY NO.: 173

DEVELOPMENTAL TOXICITY (SEGMENT II) STUDY OF WR6026 DIHYDROCHLORIDE IN RABBITS

APPENDIX C

INDIVIDUAL GRAVID UTERUS AND FETAL BODY WEIGHT DATA (GRAMS)

GROUP 3: 7 MG BASE/KG/DAY

DAM #	GRAVID UTERUS WEIGHT	MEAN FETAL WEIGHT	INDIVIDUAL FETAL WEIGHT												
			1	2	3	4	5	6	7	8	9	10	11	12	13
741	450.79	33.03	40.45M	35.58M	35.50F	39.29M	32.46M	29.13F	29.22M	29.12F	28.94M	30.59F	.	.	.
742	414.04	41.91	45.52F	43.14M	44.96M	43.74M	42.93F	L	35.90F	37.18M
743	550.52	40.72	41.89F	44.80M	38.79F	38.55M	41.14M	42.46F	40.63M	42.51M	37.75F	38.68M	.	.	.
744	465.77	37.11	38.28M	40.94F	37.15M	30.89M	31.89M	36.21F	41.62F	36.70M	40.31F
745	536.10	31.62	29.88F	33.80M	36.63M	29.68F	23.14F	31.63M	33.46F	39.62M	34.78F	31.40F	29.40F	26.01M	.
746	348.77	34.92	35.92M	34.43M	35.92M	29.12M	32.80F	38.35M	37.91M
747	347.95	36.55	43.21M	39.88M	38.05M	32.82F	32.40F	34.33M	35.15F
748	412.95	37.74	43.33F	37.41F	38.76F	41.77M	38.76F	35.68M	30.56M	35.66F
749	414.54	32.34	37.56F	33.10M	25.91F	26.42F	32.73F	39.98M	34.38F	32.22M	28.78M
750	412.19	37.67	48.36F	L	32.67F	43.55F	44.71F	37.20F	L	23.34F	L	33.87F	.	.	.
751	272.59	28.65	28.93F	29.31F	29.92F	27.18F	E	28.27M	27.26F	29.66M
752	412.61	31.06	36.91F	L	31.29F	35.89M	27.86F	25.19M	25.77F	37.94F	27.65M
753	427.07	42.93	49.67F	44.23F	38.32F	41.42M	43.22M	42.70F	40.92F
754	382.93	34.07	41.71M	34.88M	36.78M	32.33M	34.94M	21.46M	36.48F	33.97M
755	263.36	26.34	E	31.21F	27.51F	24.51F	24.67M	28.38F	25.20F	22.92F
756	SACRIFICED MORIBUND - GESTATION DAY 8														
757	378.79	34.19	37.27F	28.35F	27.13M	33.93F	33.40M	34.20M	38.00F	41.26M
758	469.38	42.12	40.64F	39.31F	41.24M	39.11F	40.67F	E	46.89F	E	44.03F	45.03M	.	.	.
759	303.21	34.72	40.30M	35.14M	28.30M	25.80F	38.22F	40.57F
760	229.33	39.75	43.93F	36.37F	42.98M	35.72F

KEY: E= EARLY RESORPTION L= LATE RESORPTION
M=MALE F=FEMALE

APPENDIX C

UIC/TRL STUDY NO.: 173

DEVELOPMENTAL TOXICITY (SEGMENT II) STUDY OF WR6026 DIHYDROCHLORIDE IN RABBITS

INDIVIDUAL GRAVID UTERUS AND FETAL BODY WEIGHT DATA (GRAMS)

GROUP 4: 15/10 MG BASE/KG/DAY*

DAM #	GRAVID MEAN		INDIVIDUAL FETAL WEIGHT												
	UTERUS WEIGHT	FETAL WEIGHT	1	2	3	4	5	6	7	8	9	10	11	12	13
761	475.97	33.21	43.51M	42.80F	26.53F	31.28F	E	43.27M	37.20M	32.91F	E	30.74M	16.34F	27.51F	.
762	531.00	34.27	42.80F	39.88F	32.43M	29.10M	35.20M	40.36M	39.25M	32.21M	29.44M	25.27F	31.06F	.	.
763	FOUND DEAD - GESTATION DAY 14														
764	FOUND DEAD - GESTATION DAY 8														
765	FOUND DEAD - GESTATION DAY 10														
766	317.23	31.24	39.06M	27.83F	28.21M	31.84M	22.26M	E	32.32F	37.15F
767	352.63	35.07	38.99M	36.01M	34.53F	34.78F	33.42M	33.98M	33.75M
768	391.78	41.53	43.89M	46.79M	33.08M	45.28M	40.66M	37.98M	43.05F
769	155.61	28.93	E	E	E	33.20M	36.21F	E	17.38M	E
770	428.61	38.95	41.56M	40.97F	37.58M	36.12F	39.44F	40.31M	38.47M	37.17F
771	371.17	36.91	41.47M	34.81M	34.88F	35.01M	41.11M	36.26F	34.83F
772	440.86	40.44	43.48F	46.54F	37.90M	34.99F	46.53M	41.30M	34.77M	38.03M
773	361.65	42.03	45.31F	46.59F	42.70M	43.18M	34.40M	39.98F
774	498.13	36.10	37.41F	39.59M	39.13F	35.39F	37.32F	33.56F	36.84F	33.20F	30.98F	37.65F	.	.	.
775	FOUND DEAD - GESTATION DAY 11														
776	562.85	31.61	34.56M	37.32F	31.80M	33.84M	37.52F	33.44M	N	19.68M	29.33M	29.62M	30.04F	30.54M	.
777	119.99	37.00	E	37.67M	E	E	E	E	36.32M
778	367.01	38.56	41.59M	36.26F	38.88M	41.74M	40.08M	33.58F	37.76F
779	402.60	39.41	42.09F	38.62M	37.24F	37.33F	44.64M	38.92F	37.02M
780	366.95	43.28	E	46.45M	E	46.27F	38.68F	43.33F	38.35F	46.61M
MEAN	384.00	36.78													
S.D.	118.11	4.18													
N	16	16													

KEY: E= EARLY RESORPTION L= LATE RESORPTION N=NON-VIABLE FETUS
M=MALE F=FEMALE

* DUE TO MORTALITY, THE HIGH DOSE WAS REDUCED FROM 15 MG BASE/KG/DAY TO 10 MG BASE/KG/DAY ON GESTATION DAYS 12-15 (THE RANGE OF DAYS REFLECTS STUDY STAGGER-START OVER 4 DAYS).

APPENDIX C

UIC/TRL STUDY NO.: 173 DEVELOPMENTAL TOXICITY (SEGMENT II) STUDY OF WR6026 DIHYDROCHLORIDE IN RABBITS

INDIVIDUAL GRAVID UTERUS AND FETAL BODY WEIGHT DATA (GRAMS)

GROUP 5: 300 MG/KG/DAY (RETINOL PALMITATE)

DAM #	GRAVID UTERUS WEIGHT	MEAN FETAL WEIGHT	INDIVIDUAL FETAL WEIGHT											
			1	2	3	4	5	6	7	8	9	10	11	12
781	506.72	32.03	23.93F	32.28F	39.98F	32.58F	E	29.89F	32.08F	35.56F	E	41.16M		
782	271.17	37.91	E	39.68F	38.00F	34.52F	36.19F	E	E	E				
783	487.11	43.26	E	49.41M	37.38M	40.43F	40.78F	41.09M	43.75M	46.92M		46.30F		
784	437.73	35.12	40.94F	39.46F	39.33M	33.01M	33.84F	30.59F	33.21M	32.12M		33.59M		
785	482.40	41.59	44.02F	44.41M	42.76M	33.61M	38.71F	E	45.91F	41.42F		41.91M		
786	83.71	37.43	E	E	E	E	E	37.43F						
787	358.91	32.33	37.44F	33.60F	31.20F	41.27F	34.37M	31.15F	26.28M	23.35M				
788	8.16	-	E	E	E	E	E	E	E					
789	188.35	39.03	E	37.99M	E	38.16M	E	40.94F	E					
790	NONGRAVID													
791	373.83	46.42	51.04M	L	46.11F	38.54F	46.31M	50.08F						
792	9.61	-	E	E	E	E	E	E						
793	349.86	36.33	E	25.39F	E	37.99F	E	33.85M	34.05M	38.54M		48.14M		
794	497.94	38.51	42.72M	38.95M	41.19M	38.94F	34.11M	37.80M	35.06F	37.67M		40.14F		
795	351.93	39.04	E	42.90M	39.44M	E	E	41.70F	36.99F	33.86F		39.32M		
796	97.96	45.46	E	45.46F	E	E	E	E	E					
797	318.78	40.76	E	E	40.34M	42.90F	E	41.86M	38.76M	39.96F				
798	367.71	43.42	E	48.08M	36.31F	40.47F	48.29F	44.64F	E	E		42.73F		
799	10.51	-	E	E	E	E	E	E						
800	387.39	34.48	40.68M	34.39M	28.77F	30.68M	38.84F	34.25M	34.12F	E		34.09F		

KEY: E= EARLY RESORPTION L= LATE RESORPTION
M=MALE F=FEMALE

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APPENDIX D

UIC/TRL STUDY NO. 173 DEVELOPMENTAL TOXICITY (SEGMENT II) STUDY OF WR6026 DIHYDROCHLORIDE IN RABBITS

INDIVIDUAL FETAL MORPHOLOGICAL OBSERVATIONS

GROUP 1: 0 MG/KG/DAY

Animal: 701		
Fetal Position: Left 02		Unique Fetal Id.: 2
RIBS		
(Skeletal) RIB 13, FULL - VARIATION; BILATERAL		
Fetal Position: Left 03		Unique Fetal Id.: 3
RIBS		
(Skeletal) RIB 13, RUDIMENTARY - VARIATION; BILATERAL (NO ARTICULATING HEAD ON LEFT)		
Fetal Position: Right 01		Unique Fetal Id.: 5
RIBS		
(Skeletal) RIB 13, FULL - VARIATION; BILATERAL		
Fetal Position: Right 03		
Late Resorption: Crown-Rump Length: 57 mm		
Fetal Position: Right 04		Unique Fetal Id.: 8
RIBS		
(Skeletal) RIB 13, FULL - VARIATION; LEFT		
Fetal Position: Right 05		Unique Fetal Id.: 9
STERNUM		
(Skeletal) STERNEBRA (E), 5-6, UNOSSIFIED - VARIATION		
Animal: 702		
Fetal Position: Left 01		Unique Fetal Id.: 1
STERNUM		
(Skeletal) STERNEBRA (E), 5-6, UNOSSIFIED - VARIATION; 5 ONLY		
Fetal Position: Right 01		Unique Fetal Id.: 2
STERNUM		
(Skeletal) STERNEBRA (E), 5-6, UNOSSIFIED - VARIATION		

APPENDIX D

UIC/1.. STUDY NO. 173 DEVELOPMENTAL TOXICITY (SEGMENT II) STUDY OF WR6026 DIHYDROCHLORIDE IN RABBITS

INDIVIDUAL FETAL MORPHOLOGICAL OBSERVATIONS

GROUP 1: 0 MG/KG/DAY

Animal: 702 (CONT.)
 Fetal Position: Right 02
 Unique Fetal Id.: 3

STERNUM

(Skeletal) STERNEBRA(E), 5-6, UNOSSIFIED - VARIATION; 5 ONLY
 Fetal Position: Right 03
 Unique Fetal Id.: 4

RIBS

(Skeletal) 7TH CERVICAL RIB, PRESENT - VARIATION; LEFT

Fetal Position:

Right 04

Unique Fetal Id.: 5

RIBS

(Skeletal) 7TH CERVICAL RIB, PRESENT - VARIATION; BILATERAL

Animal: 703

Fetal Position: Right 01

Unique Fetal Id.: 4

RIBS

(Skeletal) RIB 13, RUDIMENTARY - VARIATION; RIGHT

Fetal Position:

Right 02

Unique Fetal Id.: 5

RIBS

(Skeletal) RIB 13, FULL - VARIATION; BILATERAL

VERTEBRAL COLUMN

(Skeletal) VERTEBRAE, 27 PRESACRAL VERTEBRAE - VARIATION

Fetal Position:

Right 03

Unique Fetal Id.: 6

RIBS

(Skeletal) RIB 13, FULL - VARIATION; LEFT

Fetal Position:

Right 04

Unique Fetal Id.: 7

RIBS

(Skeletal) RIB 13, RUDIMENTARY - VARIATION; BILATERAL (RIGHT--NO ARTICULATING HEAD)

APPENDIX D

UIC/TRL STUDY NO. 173 DEVELOPMENTAL TOXICITY (SEGMENT II) STUDY OF WR6026 DIHYDROCHLORIDE IN RABBITS

INDIVIDUAL FETAL MORPHOLOGICAL OBSERVATIONS

GROUP 1: 0 MG/KG/DAY

Animal: 703 (CONT.)	Unique Fetal Id.: 9
Fetal Position: Right 06	
RIBS	
(Skeletal) RIB 13, FULL - VARIATION; LEFT	
STERNUM	
(Skeletal) STERNEBRA(E), MALALIGNED, SLIGHT TO MODERATE - VARIATION; 3, SLIGHT	
Animal: 704	Unique Fetal Id.: 1
Fetal Position: Left 01	
RIBS	
(Skeletal) RIB 13, FULL - VARIATION; BILATERAL	
Fetal Position: Left 02	Unique Fetal Id.: 2
RIBS	
(Skeletal) RIB 13, FULL - VARIATION; BILATERAL	
STERNUM	
(Skeletal) STERNEBRA(E), MALALIGNED, SLIGHT TO MODERATE - VARIATION; 5, SLIGHT	
Fetal Position: Left 03	Unique Fetal Id.: 3
RIBS	
(Skeletal) RIB 13, FULL - VARIATION; BILATERAL	
Fetal Position: Right 02	Unique Fetal Id.: 5
RIBS	
(Skeletal) RIB 13, FULL - VARIATION; BILATERAL	
Fetal Position: Right 03	Unique Fetal Id.: 6
RIBS	
(Skeletal) RIB 13, FULL - VARIATION; BILATERAL	
Fetal Position: Right 04	Unique Fetal Id.: 7
RIBS	
(Skeletal) RIB 13, FULL - VARIATION; BILATERAL	
VERTEBRAL COLUMN (Skeletal) VERTEBRAE, 27 PRESACRAL VERTEBRAE - VARIATION	

APPENDIX D

UIC/TRL STUDY NO. 173 DEVELOPMENTAL TOXICITY (SEGMENT II) STUDY OF WR6026 DIHYDROCHLORIDE IN RABBITS
INDIVIDUAL FETAL MORPHOLOGICAL OBSERVATIONS

GROUP 1: 0 MG/KG/DAY

Animal: 705
Fetal Position: Left 02 Unique Fetal Id.: 2
RIBS (Skeletal) RIB 13, FULL - VARIATION; LEFT

Fetal Position: Left 03 Unique Fetal Id.: 3
RIBS (Skeletal) RIB 13, FULL - VARIATION; BILATERAL

Fetal Position: Left 04 Unique Fetal Id.: 4

RIBS (Skeletal) RIB 13, FULL - VARIATION; BILATERAL

Fetal Position: Right 02
Late Resorption: Crown-Rump Length: 55 mm

Fetal Position: Right 03 Unique Fetal Id.: 7
STERNUM (Skeletal) STERNEBRA(E), MALALIGNED, SLIGHT TO MODERATE - VARIATION;
5, SLIGHT

Animal: 706
Fetal Position: Left 01 Unique Fetal Id.: 1
RIBS (Skeletal) RIB 13, FULL - VARIATION; BILATERAL

STERNUM (Skeletal) STERNEBRA(E), MALALIGNED, SLIGHT TO MODERATE - VARIATION; 2-5, SLIGHT

VERTEBRAL COLUMN (Skeletal) VERTEBRAE, 27 PRESACRAL VERTEBRAE - VARIATION

HINDLIMBS (Skeletal) TALUS, UNOSSIFIED - VARIATION; LEFT

APPENDIX D

UIC/TRL STUDY NO. 173 DEVELOPMENTAL TOXICITY (SEGMENT II) STUDY OF WR6026 DIHYDROCHLORIDE IN RABBITS

INDIVIDUAL FETAL MORPHOLOGICAL OBSERVATIONS

GROUP 1: 0 MG/KG/DAY

Animal: 706 (CONT.)	
Fetal Position: Right 01	Unique Fetal Id.: 2
RIBS	
(Skeletal) RIB 13, FULL - VARIATION; BILATERAL	
Fetal Position: Right 02	Unique Fetal Id.: 3
RIBS	
(Skeletal) RIB 13, FULL - VARIATION; RIGHT	
Fetal Position: Right 03	Unique Fetal Id.: 4
RIBS	
(Skeletal) RIB 13, FULL - VARIATION; BILATERAL	
Fetal Position: Right 04	Unique Fetal Id.: 5
RIBS	
(Skeletal) RIB 13, FULL - VARIATION; LEFT FULL, RIGHT RUDIMENTARY	
VERTEBRAL COLUMN	
(Skeletal) VERTEBRAE, 27 PRESACRAL VERTEBRAE - VARIATION	
Fetal Position: Right 05	Unique Fetal Id.: 6
RIBS	
(Skeletal) RIB 13, RUDIMENTARY - VARIATION; BILATERAL	
Fetal Position: Right 06	Unique Fetal Id.: 7
RIBS	
(Skeletal) RIB 13, FULL - VARIATION; BILATERAL	
STERNUM	
(Skeletal) STERNEBRA (E), MALALIGNED, SLIGHT TO MODERATE - VARIATION; 2, 3 AND 4, SLIGHT	
VERTEBRAL COLUMN	
(Skeletal) VERTEBRAE, 27 PRESACRAL VERTEBRAE - VARIATION	
Fetal Position: Right 07	Unique Fetal Id.: 8
RIBS	
(Skeletal) RIB 13, RUDIMENTARY - VARIATION; BILATERAL	

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UIC/TRL STUDY NO. 173 DEVELOPMENTAL TOXICITY (SEGMENT II) STUDY OF WR6026 DIHYDROCHLORIDE IN RABBITS

INDIVIDUAL FETAL MORPHOLOGICAL OBSERVATIONS

GROUP 1: 0 MG/KG/DAY

Animal: 707		
Fetal Position:	Left 02	Unique Fetal Id.: 2
STERNUM		
(Skeletal)	STERNEBRA (E), MALALIGNED, SLIGHT TO MODERATE - VARIATION;	
	4, SLIGHT	
	STERNEBRA (E), 5-6, UNOSSIFIED - VARIATION; 5 ONLY	
Fetal Position:	Right 01	Unique Fetal Id.: 3
RIBS	(Skeletal) RIB 13, FULL - VARIATION; LEFT RUDIMENTARY, RIGHT FULL	
VERTEBRAL COLUMN		
(Skeletal)	VERTEBRAE, 27 PRESACRAL VERTEBRAE - VARIATION	
Fetal Position:	Right 02	Unique Fetal Id.: 4
THORACIC CAVITY		
(Visceral)	HEART, MAJOR BLOOD VESSEL, VARIATION - VARIATION; LEFT	
	CAROTID ARISES FROM THE BRACHIOCEPHALIC TRUNK	
Fetal Position:	Right 04	Unique Fetal Id.: 6
STERNUM		
(Skeletal)	STERNEBRA (E), 5-6, UNOSSIFIED - VARIATION; 5 ONLY	
Fetal Position:	Right 05	Unique Fetal Id.: 7
STERNUM		
(Skeletal)	STERNEBRA (E), 5-6, UNOSSIFIED - VARIATION; 5 ONLY	
Fetal Position:	Right 06	Unique Fetal Id.: 8
RIBS	(Skeletal) RIB 13, RUDIMENTARY - VARIATION; LEFT (NO ARTICULATING	
	HEAD)	
Animal: 708		
Fetal Position:	Left 01	Unique Fetal Id.: 1
THORACIC CAVITY		
(Visceral)	HEART, MAJOR BLOOD VESSEL, VARIATION - VARIATION;	
	ACCESSORY LEFT SUBCLAVIAN	

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UIC/TRL STUDY NO. 173 DEVELOPMENTAL TOXICITY (SEGMENT II) STUDY OF WR6026 DIHYDROCHLORIDE IN RABBITS

INDIVIDUAL FETAL MORPHOLOGICAL OBSERVATIONS

GROUP 1: 0 MG/KG/DAY

Animal: 708 (CONT.)		
Fetal Position: Left 02		Unique Fetal Id.: 2
RIBS		
(Skeletal) RIB 13, FULL - VARIATION; RIGHT		
Fetal Position: Left 03		Unique Fetal Id.: 3
RIBS		
(Skeletal) RIB 13, RUDIMENTARY - VARIATION; BILATERAL (RIGHT--NO ARTICULATING HEAD)		
Fetal Position: Left 04		Unique Fetal Id.: 4
RIBS		
(Skeletal) RIB 13, RUDIMENTARY - VARIATION; RIGHT (NO ARTICULATING HEAD)		
SKULL		
(Skeletal) HYOID ARCH(ES), BENT - VARIATION; RIGHT, SLIGHT		
Fetal Position: Right 04		Unique Fetal Id.: 8
RIBS		
(Skeletal) RIB 13, FULL - VARIATION; RIGHT		
Animal: 709		
Fetal Position: Left 01		Unique Fetal Id.: 1
RIBS		
(Skeletal) RIB 13, FULL - VARIATION; BILATERAL		
STERNUM		
(Skeletal) STERNEBRA(E), MALALIGNED, SLIGHT TO MODERATE - VARIATION; 4 AND 5, SLIGHT		
Fetal Position: Left 02		Unique Fetal Id.: 2
RIBS		
(Skeletal) RIB 13, FULL - VARIATION; BILATERAL		

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UIC/TRL STUDY NO. 173 DEVELOPMENTAL TOXICITY (SEGMENT II) STUDY OF WR6026 DIHYDROCHLORIDE IN RABBITS
INDIVIDUAL FETAL MORPHOLOGICAL OBSERVATIONS

GROUP 1: 0 MG/KG/DAY

Animal: 709 (CONT.)
Fetal Position: Left 03 Unique Fetal Id.: 3
RIBS

(Skeletal) RIB 13, FULL - VARIATION; BILATERAL

Fetal Position: Right 01 Unique Fetal Id.: 4
RIBS

(Skeletal) RIB 13, FULL - VARIATION; BILATERAL

VERTEBRAL COLUMN

(Skeletal) VERTEBRAE, 27 PRESACRAL VERTEBRAE - VARIATION

Fetal Position: Right 02 Unique Fetal Id.: 5
RIBS

(Skeletal) RIB 13, FULL - VARIATION; BILATERAL

STERNUM

(Skeletal) STERNEBRA (2), MALALIGNED, SLIGHT TO MODERATE - VARIATION;
5, SLIGHT

Fetal Position: Right 04 Unique Fetal Id.: 7
RIBS

(Skeletal) RIB 13, RUDIMENTARY - VARIATION; BILATERAL

SKULL

(Skeletal) HYOID BODY, UNOSSIFIED - VARIATION

Fetal Position: Right 05 Unique Fetal Id.: 8
RIBS

(Skeletal) RIB 13, FULL - VARIATION; BILATERAL

VERTEBRAL COLUMN

(Skeletal) VERTEBRAE, 27 PRESACRAL VERTEBRAE - VARIATION

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UIC/TRL STUDY NO. 173 DEVELOPMENTAL TOXICITY (SEGMENT II) STUDY OF WR6026 DIHYDROCHLORIDE IN RABBITS

INDIVIDUAL FETAL MORPHOLOGICAL OBSERVATIONS

GROUP 1: 0 MG/KG/DAY

Animal: 710			
Fetal Position: Left 01		Unique Fetal Id.: 1	
RIBS			
(Skeletal) RIB 13, FULL - VARIATION; BILATERAL			
VERTEBRAL COLUMN			
(Skeletal) VERTEBRAE, 27 PRESACRAL VERTEBRAE - VARIATION			
Fetal Position: Left 02		Unique Fetal Id.: 2	
RIBS			
(Skeletal) RIB 13, RUDIMENTARY - VARIATION; RIGHT			
Fetal Position: Left 03		Unique Fetal Id.: 3	
RIBS			
(Skeletal) RIB 13, RUDIMENTARY - VARIATION; BILATERAL			
Fetal Position: Left 06		Unique Fetal Id.: 6	
RIBS			
(Skeletal) RIB 13, FULL - VARIATION; LEFT FULL, RIGHT RUDIMENTARY			
Fetal Position: Left 07		Unique Fetal Id.: 7	
STERNUM			
(Skeletal) STERNEBRA(E), MALALIGNED, SLIGHT TO MODERATE - VARIATION; 4 AND 5, SLIGHT			
Fetal Position: Right 02		Unique Fetal Id.: 9	
RIBS			
(Skeletal) RIB 13, FULL - VARIATION; RIGHT			
STERNUM			
(Skeletal) STERNEBRA(E), MALALIGNED, SLIGHT TO MODERATE - VARIATION; 2-5, SLIGHT			
Animal: 711			
Fetal Position: Left 01		Unique Fetal Id.: 1	
RIBS			
(Skeletal) RIB 13, RUDIMENTARY - VARIATION; RIGHT			

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UIC/TRL STUDY NO. 173 DEVELOPMENTAL TOXICITY (SEGMENT II) STUDY OF WR6026 DIHYDROCHLORIDE IN RABBITS

INDIVIDUAL FETAL MORPHOLOGICAL OBSERVATIONS

GROUP 1: 0 MG/KG/DAY

Animal: 711 (CONT.) Unique Fetal Id.: 2
 Fetal Position: Left 02
 RIBS (Skeletal) RIB 13, FULL - VARIATION; BILATERAL

VERTEBRAL COLUMN
 (Skeletal) VERTEBRAE, 27 PRESACRAL VERTEBRAE - VARIATION

Fetal Position: Left 03 Unique Fetal Id.: 3
 RIBS (Skeletal) RIB 13, FULL - VARIATION; BILATERAL

STERNUM
 (Skeletal) STERNEBRA(E), 5-6, UNOSSIFIED - VARIATION; 5 ONLY

VERTEBRAL COLUMN
 (Skeletal) VERTEBRAE, 27 PRESACRAL VERTEBRAE - VARIATION

Fetal Position: Right 01 Unique Fetal Id.: 4
 RIBS (Skeletal) RIB 13, RUDIMENTARY - VARIATION; LEFT (NO ARTICULATING HEAD)

Fetal Position: Right 02 Unique Fetal Id.: 5
 RIBS (Skeletal) RIB 13, FULL - VARIATION; BILATERAL (RIGHT--SMALL ARTICULATING HEAD)

VERTEBRAL COLUMN
 (Skeletal) VERTEBRAE, 27 PRESACRAL VERTEBRAE - VARIATION

Animal: 712 Unique Fetal Id.: 1
 Fetal Position: Left 01
 RIBS (Skeletal) RIB 13, RUDIMENTARY - VARIATION; LEFT (NO ARTICULATING HEAD)

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INDIVIDUAL FETAL MORPHOLOGICAL OBSERVATIONS

GROUP 1: 0 MG/KG/DAY

Animal: 712 (CONT.)	Unique Fetal Id.: 2
Fetal Position: Left 02	
RIBS	
(Skeletal) RIB 13, RUDIMENTARY - VARIATION; LEFT (NO ARTICULATING HEAD)	
7TH CERVICAL RIB, PRESENT - VARIATION; LEFT	
Fetal Position: Left 03	Unique Fetal Id.: 3
RIBS	
(Skeletal) RIB 13, FULL - VARIATION; LEFT RUDIMENTARY (NO ARTICULATING HEAD), RIGHT FULL	
Animal: 713	Unique Fetal Id.: 1
Fetal Position: Left 01	
RIBS	
(Skeletal) RIB 13, RUDIMENTARY - VARIATION; LEFT	
STERNUM	
(Skeletal) STERNEBRA(E), 5-6, UNOSSIFIED - VARIATION	
ABDOMEN	
(Visceral) KIDNEY(S), HYDRONEPHROSIS - VARIATION; RIGHT, SLIGHT URETER(S), DISTENDED - VARIATION; RIGHT, SLIGHT KIDNEY(S) AND/OR URETER(S), ANOMALY - MALFORMATION; LEFT KIDNEY SMALL, MALFORMED, UNASCENDED	
Fetal Position: Left 03	Unique Fetal Id.: 3
RIBS	
(Skeletal) 7TH CERVICAL RIB, PRESENT - VARIATION; LEFT	
STERNUM	
(Skeletal) STERNEBRA(E), 5-6, UNOSSIFIED - VARIATION	
HEAD	
(External) FACE, FACIAL BLEB(S) - MALFORMATION; LEFT SIDE	

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UIC/TRL STUDY NO. 173 DEVELOPMENTAL TOXICITY (SEGMENT II) STUDY OF WR6026 DIHYDROCHLORIDE IN RABBITS

INDIVIDUAL FETAL MORPHOLOGICAL OBSERVATIONS

GROUP 1: 0 MG/KG/DAY

Animal: 713 (CONT.)	Unique Fetal Id.: 4
Fetal Position: Left 04	
THORACIC CAVITY	
(Visceral)	HEART, MAJOR BLOOD VESSEL, VARIATION - VARIATION;
	RETROESOPHAGEAL RIGHT SUBCLAVIAN
RIBS	
(Skeletal)	7TH CERVICAL RIB, PRESENT - VARIATION; BILATERAL
STERNUM	
(Skeletal)	STERNEBRA(E), 5-6, UNOSSIFIED - VARIATION; 6 ONLY
SKULL	
(Skeletal)	HYOID ARCH(ES), UNOSSIFIED - VARIATION; LEFT
ABDOMEN	
(Visceral)	URETER(S), RETROCAVAL - VARIATION; RIGHT
Fetal Position: Left 05	Unique Fetal Id.: 5
RIBS	
(Skeletal)	7TH CERVICAL RIB, PRESENT - VARIATION; BILATERAL
Fetal Position: Right 02	Unique Fetal Id.: 7
STERNUM	
(Skeletal)	STERNEBRA(E), MALALIGNED, SLIGHT TO MODERATE - VARIATION; 3 and 4, SLIGHT
Fetal Position: Right 03	Unique Fetal Id.: 8
RIBS	
(Skeletal)	RIB 13, FULL - VARIATION; LEFT
STERNUM	
(Skeletal)	STERNEBRA(E), 5-6, UNOSSIFIED - VARIATION; 5 ONLY

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INDIVIDUAL FETAL MORPHOLOGICAL OBSERVATIONS

GROUP 1: 0 MG/KG/DAY

Animal: 714		Unique Fetal Id.: 1
Fetal Position: Left 01		
THORACIC CAVITY (Visceral)	HEART, MAJOR BLOOD VESSEL, VARIATION - VARIATION; LEFT CAROTID ARISES FROM THE BRACHIOCEPHALIC TRUNK	
RIBS		
	(Skeletal) RIB 13, RUDIMENTARY - VARIATION; RIGHT (NO ARTICULATING HEAD)	
STERNUM		
	(Skeletal) STERNEBRA(E), MALALIGNED, SLIGHT TO MODERATE - VARIATION; 5, SLIGHT	
VERTEBRAL COLUMN		
	(Skeletal) VERTEBRAE, 27 PRESACRAL VERTEBRAE - VARIATION	
Fetal Position: Left 02		Unique Fetal Id.: 2
THORACIC CAVITY (Visceral)	HEART, MAJOR BLOOD VESSEL, VARIATION - VARIATION; LEFT CAROTID ARISES FROM THE BRACHIOCEPHALIC TRUNK	
STERNUM		
	(Skeletal) STERNEBRA(E), MALALIGNED, SLIGHT TO MODERATE - VARIATION; 2-5, SLIGHT	
Fetal Position: Left 03		Unique Fetal Id.: 3
THORACIC CAVITY (Visceral)	HEART, MAJOR BLOOD VESSEL, VARIATION - VARIATION; LEFT CAROTID ARISES FROM THE BRACHIOCEPHALIC TRUNK	
Fetal Position: Left 04		Unique Fetal Id.: 4
THORACIC CAVITY (Visceral)	HEART, MAJOR BLOOD VESSEL, VARIATION - VARIATION; LEFT CAROTID ARISES FROM THE BRACHIOCEPHALIC TRUNK	
RIBS		
	(Skeletal) RIB 13, FULL - VARIATION; BILATERAL	
VERTEBRAL COLUMN		
	(Skeletal) VERTEBRAE, 27 PRESACRAL VERTEBRAE - VARIATION	

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INDIVIDUAL FETAL MORPHOLOGICAL OBSERVATIONS

GROUP 1: 0 MG/KG/DAY

Animal: 714 (CONT.)
Fetal Position: Left 05 Unique Fetal Id.: 5
THORACIC CAVITY
(Visceral) HEART, MAJOR BLOOD VESSEL, VARIATION - VARIATION; LEFT
CAROTID ARISES FROM THE BRACHIOCEPHALIC TRUNK

RIBS
(Skeletal) RIB 13, FULL - VARIATION; BILATERAL

VERTEBRAL COLUMN
(Skeletal) VERTEBRAE, 27 PRESACRAL VERTEBRAE - VARIATION

Fetal Position: Left 06 Unique Fetal Id.: 6
THORACIC CAVITY
(Visceral) HEART, MAJOR BLOOD VESSEL, VARIATION - VARIATION; LEFT
CAROTID ARISES FROM THE BRACHIOCEPHALIC TRUNK

RIBS
(Skeletal) RIB 13, FULL - VARIATION; BILATERAL

VERTEBRAL COLUMN
(Skeletal) VERTEBRAE, 27 PRESACRAL VERTEBRAE - VARIATION

Fetal Position: Right 01 Unique Fetal Id.: 7
THORACIC CAVITY
(Visceral) HEART, MAJOR BLOOD VESSEL, VARIATION - VARIATION; LEFT
CAROTID ARISES FROM THE BRACHIOCEPHALIC TRUNK

Fetal Position: Right 02 Unique Fetal Id.: 8
THORACIC CAVITY
(Visceral) HEART, MAJOR BLOOD VESSEL, VARIATION - VARIATION; LEFT
CAROTID ARISES FROM THE BRACHIOCEPHALIC TRUNK

RIBS
(Skeletal) RIB 13, RUDIMENTARY - VARIATION; LEFT (NO ARTICULATING HEAD)
VERTEBRAL COLUMN
(Skeletal) VERTEBRAE, 27 PRESACRAL VERTEBRAE - VARIATION

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UIC/TRL STUDY NO. 173 DEVELOPMENTAL TOXICITY (SEGMENT II) STUDY OF WR6026 DIHYDROCHLORIDE IN RABBITS

INDIVIDUAL FETAL MORPHOLOGICAL OBSERVATIONS

GROUP 1: 0 MG/KG/DAY

Animal: 714 (CONT.)		Unique Fetal Id.: 9
Fetal Position: Right 03		
THORACIC CAVITY		
(Visceral)	HEART, MAJOR BLOOD VESSEL, VARIATION - VARIATION, LEFT	
	CAROTID ARISES FROM THE BRACHIOCEPHALIC TRUNK	
Animal: 715		
Fetal Position: Left 01		Unique Fetal Id.: 1
RIBS		
(Skeletal) RIB 13, RUDIMENTARY - VARIATION, RIGHT (NO ARTICULATING HEAD)		
Fetal Position: Right 02		Unique Fetal Id.: 4
THORACIC CAVITY		
(Visceral)	HEART, MAJOR BLOOD VESSEL, VARIATION - VARIATION, LEFT	
	CAROTID ARISES FROM THE BRACHIOCEPHALIC TRUNK	
RIBS		
(Skeletal) RIB 13, FULL - VARIATION; BILATERAL		
ABDOMEN		
(Visceral) KIDNEY(S), HYDRONEPHROSIS - VARIATION; RIGHT, SLIGHT		
URETER(S), RETROCAVAL - VARIATION; RIGHT		
Fetal Position: Right 03		Unique Fetal Id.: 5
STERNUM		
(Skeletal) STERNEBRA(E), FUSED - MALFORMATION; 4 AND 5		
Fetal Position: Right 04		Unique Fetal Id.: 6
STERNUM		
(Skeletal) STERNEBRA(E), FUSED - MALFORMATION; 3, 4 AND 5		
Fetal Position: Right 05		Unique Fetal Id.: 7
RIBS		
(Skeletal) RIB 13, RUDIMENTARY - VARIATION, LEFT		

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INDIVIDUAL FETAL MORPHOLOGICAL OBSERVATIONS

GROUP 1: 0 MG/KG/DAY

Animal: 715 (CONT.)	Unique Fetal Id.: 8
Fetal Position: Right 06	
THORACIC CAVITY	
(Visceral) HEART, MAJOR BLOOD VESSEL, VARIATION - VARIATION; LEFT	
CAROTID ARISES FROM THE BRACHIOCEPHALIC TRUNK	
ABDOMEN	
(Visceral) URETER(S), RETROCAVAL - VARIATION; RIGHT	
Animal: 716	Unique Fetal Id.: 1
Fetal Position: Left 01	
RIBS	
(Skeletal) RIB 13, FULL - VARIATION; BILATERAL	
Fetal Position: Left 02	Unique Fetal Id.: 2
RIBS	
(Skeletal) RIB 13, FULL - VARIATION; BILATERAL	
VERTEBRAL COLUMN	
(Skeletal) VERTEBRAE, 27 PRESACRAL VERTEBRAE - VARIATION	
Fetal Position: Left 03	Unique Fetal Id.: 3
RIBS	
(Skeletal) 7TH CERVICAL RIB, PRESENT - VARIATION; RIGHT	
Fetal Position: Right 02	Unique Fetal Id.: 5
RIBS	
(Skeletal) RIB 13, RUDIMENTARY - VARIATION; LEFT (NO ARTICULATING HEAD)	
Animal: 717	Unique Fetal Id.: 1
Fetal Position: Left 01	
RIBS	
(Skeletal) RIB 13, FULL - VARIATION; BILATERAL	

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INDIVIDUAL FETAL MORPHOLOGICAL OBSERVATIONS

GROUP 1: 0 MG/KG/DAY

Animal: 717 (CONT.)		
Fetal Position: Left 02		Unique Fetal Id.: 2
RIBS		
(Skeletal) RIB 13, FULL - VARIATION; BILATERAL		
VERTEBRAL COLUMN		
(Skeletal) VERTEBRAE, 27 PRESACRAL VERTEBRAE - VARIATION		
Fetal Position: Left 03		Unique Fetal Id.: 3
RIBS		
(Skeletal) RIB 13, RUDIMENTARY - VARIATION; BILATERAL		
Fetal Position: Left 04		Unique Fetal Id.: 4
STERNUM		
(Skeletal) STERNEBRA(E), MALALIGNED, SLIGHT TO MODERATE - VARIATION; 4 AND 5, SLIGHT		
Fetal Position: Right 01		Unique Fetal Id.: 5
STERNUM		
(Skeletal) STERNEBRA(E), MALALIGNED, SLIGHT TO MODERATE - VARIATION; 5, SLIGHT		
Fetal Position: Right 02		Unique Fetal Id.: 6
RIBS		
(Skeletal) RIB 13, RUDIMENTARY - VARIATION; RIGHT		
Animal: 718		
Fetal Position: Right 03		Unique Fetal Id.: 4
RIBS		
(Skeletal) RIB 13, FULL - VARIATION; LEFT RUDIMENTARY, RIGHT FULL		

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INDIVIDUAL FETAL MORPHOLOGICAL OBSERVATIONS

GROUP 1: 0 MG/KG/DAY

Animal: 719		Unique Fetal Id.: 4
Fetal Position: Left 04		
STERNUM		
(Skeletal) STERNEBRA(E), 5-6, UNOSSIFIED - VARIATION; 5 ONLY		
SKULL		
(Skeletal) HYOID ARCH(ES), BENT - VARIATION; RIGHT, MODERATE		
HINDLIMBS		
(Skeletal) TALUS, UNOSSIFIED - VARIATION; BILATERAL		
Fetal Position: Left 05		Unique Fetal Id.: 5
RIBS		
(Skeletal) RIB 13, FULL - VARIATION; LEFT RUDIMENTARY (NO ARTICULATING HEAD), RIGHT FULL		
VERTEBRAL COLUMN		
(Skeletal) VERTEBRAE, 27 PRESACRAL VERTEBRAE - VARIATION		
Fetal Position: Left 06		Unique Fetal Id.: 6
RIBS		
(Skeletal) RIB 13, FULL - VARIATION; BILATERAL		
Fetal Position: Left 07		Unique Fetal Id.: 7
RIBS		
(Skeletal) RIB 13, FULL - VARIATION; BILATERAL		
VERTEBRAL COLUMN		
(Skeletal) VERTEBRAE, 27 PRESACRAL VERTEBRAE - VARIATION		
Fetal Position: Right 01		Unique Fetal Id.: 8
RIBS		
(Skeletal) RIB 13, FULL - VARIATION; BILATERAL		
VERTEBRAL COLUMN		
(Skeletal) VERTEBRAE, 27 PRESACRAL VERTEBRAE - VARIATION		

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INDIVIDUAL FETAL MORPHOLOGICAL OBSERVATIONS

GROUP 1: 0 MG/KG/DAY

Animal: 719 (CONT.)		
Fetal Position: Right 02		Unique Fetal Id.: 9
RIBS		
(Skeletal) RIB 13, RUDIMENTARY - VARIATION; RIGHT (NO ARTICULATING HEAD)		
Animal: 720		
Fetal Position: Left 01		Unique Fetal Id.: 1
STERNUM		
(Skeletal) STERNEBRA (E), FUSED - MALFORMATION; 4 AND 5		
Fetal Position: Left 07		Unique Fetal Id.: 7
RIBS		
(Skeletal) RIB 13, RUDIMENTARY - VARIATION; BILATERAL (RIGHT--NO ARTICULATING HEAD)		
Fetal Position: Right 01		Unique Fetal Id.: 8
RIBS		
(Skeletal) RIB 13, RUDIMENTARY - VARIATION; RIGHT		
Fetal Position: Right 02		Unique Fetal Id.: 9
RIBS		
(Skeletal) RIB 13, FULL - VARIATION; RIGHT		

Note: For Dam 720, Fetus 9, a visceral examination of the thoracic cavity and organs was not performed.

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INDIVIDUAL FETAL MORPHOLOGICAL OBSERVATIONS

GROUP 2: 3 MG BASE/KG/DAY

Animal: 721	Unique Fetal Id.: 2
Fetal Position: Left 02	
RIBS	
(Skeletal) RIB 13, RUDIMENTARY - VARIATION; RIGHT (SMALL ARTICULATING HEAD)	
VERTEBRAL COLUMN	
(Skeletal) VERTEBRAE, 27 PRESACRAL VERTEBRAE - VARIATION	
Fetal Position: Right 01	Unique Fetal Id.: 4
STERNUM	
(Skeletal) STERNEBRA(E), MALALIGNED, SLIGHT TO MODERATE - VARIATION; 5, SLIGHT	
STERNEBRA(E), 5-6, UNOSSIFIED - VARIATION; 6 ONLY	
Fetal Position: Right 03	Unique Fetal Id.: 6
RIBS	
(Skeletal) RIB 13, FULL - VARIATION; BILATERAL	
STERNUM	
(Skeletal) STERNEBRA(E), 5-6, UNOSSIFIED - VARIATION; 6 ONLY	
VERTEBRAL COLUMN	
(Skeletal) VERTEBRAE, 27 PRESACRAL VERTEBRAE - VARIATION	
Fetal Position: Right 04	Unique Fetal Id.: 7
THORACIC CAVITY	
(Visceral) HEART, HEART AND/OR GREAT VESSEL, ANOMALY - MALFORMATION; ENLARGED; LEFT ATRIUM ENLARGED	
STERNUM	
(Skeletal) STERNEBRA(E), 5-6, UNOSSIFIED - VARIATION; 6 ONLY	
VERTEBRAL COLUMN	
(Skeletal) VERTEBRAE, 27 PRESACRAL VERTEBRAE - VARIATION	

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INDIVIDUAL FETAL MORPHOLOGICAL OBSERVATIONS

GROUP 2: 3 MG BASE/KG/DAY

Animal: 721 (CONT.)	Unique Fetal Id.: 8
Fetal Position: Right 05	
RIBS	
(Skeletal) RIB 13, FULL - VARIATION; LEFT	
VERTEBRAL COLUMN	
(Skeletal) VERTEBRAE, 27 PRESACRAL VERTEBRAE - VARIATION	
Fetal Position: Right 06	Unique Fetal Id.: 9
SKULL	
(Skeletal) HYOID ARCH(ES), BENT - VARIATION; RIGHT, MODERATE	
Fetal Position: Right 07	Unique Fetal Id.: 10
SKULL	
(Skeletal) HYOID ARCH(ES), BENT - VARIATION; BILATERAL, MODERATE	
Fetal Position: Right 08	Unique Fetal Id.: 11
VERTEBRAL COLUMN	
(Skeletal) VERTEBRAE, 27 PRESACRAL VERTEBRAE - VARIATION	
Animal: 722	
Fetal Position: Left 01	Unique Fetal Id.: 1
RIBS	
(Skeletal) RIB 13, FULL - VARIATION; LEFT FULL, RIGHT RUDIMENTARY (NO ARTICULATING HEAD)	
Fetal Position: Left 02	Unique Fetal Id.: 2
STERNUM	
(Skeletal) STERNEBRA(E), MALALIGNED, SLIGHT TO MODERATE - VARIATION; 2-5, SLIGHT	
Fetal Position: Right 01	Unique Fetal Id.: 3
RIBS	
(Skeletal) RIB 13, FULL - VARIATION; LEFT	

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INDIVIDUAL FETAL MORPHOLOGICAL OBSERVATIONS

GROUP 2: 3 MG BASE/KG/DAY

Animal: 722 (CONT.)		Unique Fetal Id.: 4
Fetal Position: Right 02		
THORACIC CAVITY		
(Visceral)	HEART, MAJOR BLOOD VESSEL, VARIATION - VARIATION; LEFT	
	CAROTID ARISES FROM BRACHIOCEPHALIC TRUNK	
RIBS		
(Skeletal)	RIB 13, FULL - VARIATION; BILATERAL	
Fetal Position: Right 03		Unique Fetal Id.: 5
STERNUM		
(Skeletal)	STERNEBRA(E), MALALIGNED AND FUSED - MALFORMATION; 4 AND 5 FUSED; 2-5, MALALIGNED SLIGHT	
Fetal Position: Right 04		Unique Fetal Id.: 6
THORACIC CAVITY		
(Visceral)	HEART, MAJOR BLOOD VESSEL, VARIATION - VARIATION; LEFT	
	CAROTID ARISES FROM BRACHIOCEPHALIC TRUNK	
Fetal Position: Right 05		Unique Fetal Id.: 7
RIBS		
(Skeletal)	RIB 13, FULL - VARIATION; BILATERAL	
Fetal Position: Right 06		Unique Fetal Id.: 8
RIBS		
(Skeletal)	RIB 13, RUDIMENTARY - VARIATION; LEFT (NO ARTICULATING HEAD)	
Animal: 723		
Fetal Position: Left 01		Unique Fetal Id.: 1
RIBS		
(Skeletal)	RIB 13, FULL - VARIATION; RIGHT	
STERNUM		
(Skeletal)	STERNEBRA(E), 5-6, UNOSSIFIED - VARIATION; 6 ONLY	
VERTEBRAL COLUMN		
(Skeletal)	VERTEBRAE, 27 PRESACRAL VERTEBRAE - VARIATION	

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UIC/TRL STUDY NO. 173 DEVELOPMENTAL TOXICITY (SEGMENT II) STUDY OF WR6026 DIHYDROCHLORIDE IN RABBITS

INDIVIDUAL FETAL MORPHOLOGICAL OBSERVATIONS

GROUP 2: 3 MG BASE/KG/DAY

Animal: 723 (CONT.)	Unique Fetal Id.: 2
Fetal Position: Left 02	
RIBS	
(Skeletal) RIB 13, RUDIMENTARY - VARIATION; RIGHT (NO ARTICULATING HEAD)	
Fetal Position: Left 03	Unique Fetal Id.: 3
RIBS	
(Skeletal) RIB 13, FULL - VARIATION; BILATERAL	
VERTEBRAL COLUMN	
(Skeletal) VERTEBRAE, 27 PRESACRAL VERTEBRAE - VARIATION	
Fetal Position: Right 01	Unique Fetal Id.: 5
RIBS	
(Skeletal) RIB 13, FULL - VARIATION; BILATERAL	
STERNUM	
(Skeletal) STERNEBRA(E), 5-6, UNOSSIFIED - VARIATION	
Fetal Position: Right 03	Unique Fetal Id.: 7
STERNUM	
(Skeletal) STERNEBRA(E), 5-6, UNOSSIFIED - VARIATION; 5 ONLY	
Fetal Position: Right 04	Unique Fetal Id.: 8
RIBS	
(Skeletal) RIB 13, FULL - VARIATION; BILATERAL	
VERTEBRAL COLUMN	
(Skeletal) VERTEBRAE, 27 PRESACRAL VERTEBRAE - VARIATION	
Fetal Position: Right 05	Unique Fetal Id.: 9
RIBS	
(Skeletal) RIB 13, RUDIMENTARY - VARIATION; LEFT (NO ARTICULATING HEAD)	
STERNUM	
(Skeletal) STERNEBRA(E), MALALIGNED, SLIGHT TO MODERATE - VARIATION; 3 AND 4, SLIGHT	
STERNEBRA(E), 5-6, UNOSSIFIED - VARIATION	

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UIC/TRL STUDY NO. 173 DEVELOPMENTAL TOXICITY (SEGMENT II) STUDY OF WR6026 DIHYDROCHLORIDE IN RABBITS
INDIVIDUAL FETAL MORPHOLOGICAL OBSERVATIONS

GROUP 2: 3 MG BASE/KG/DAY

Animal: 723 (CONT.)		Unique Fetal Id.: 10
Fetal Position: Right 06		
RIBS		
(Skeletal) RIB 13, FULL - VARIATION; BILATERAL		
Fetal Position: Right 07		Unique Fetal Id.: 11
RIBS		
(Skeletal) RIB 13, FULL - VARIATION; BILATERAL		
STERNUM		
(Skeletal) STERNEBRA(E), 5-6, UNOSSIFIED - VARIATION		
VERTEBRAL COLUMN		
(Skeletal) VERTEBRAE, 27 PRESACRAL VERTEBRAE - VARIATION		
Fetal Position: Right 08		Unique Fetal Id.: 12
RIBS		
(Skeletal) RIB 13, FULL - VARIATION; BILATERAL		
STERNUM		
(Skeletal) STERNEBRA(E), 5-6, UNOSSIFIED - VARIATION		
VERTEBRAL COLUMN		
(Skeletal) VERTEBRAE, 27 PRESACRAL VERTEBRAE - VARIATION		
Animal: 724		
Fetal Position: Left 01		Unique Fetal Id.: 1
RIBS		
(Skeletal) RIB 13, RUDIMENTARY - VARIATION; LEFT		
STERNUM		
(Skeletal) STERNEBRA(E), 5-6, UNOSSIFIED - VARIATION; 5 ONLY		
VERTEBRAL COLUMN		
(Skeletal) VERTEBRAE, 27 PRESACRAL VERTEBRAE - VARIATION		

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INDIVIDUAL FETAL MORPHOLOGICAL OBSERVATIONS

GROUP 2: 3 MG BASE/KG/DAY

Animal: 724 (CONT.)	Unique Fetal Id.: 2
Fetal Position: Left 02	
RIBS	
(Skeletal) RIB 13, FULL - VARIATION, BILATERAL	
STERNUM	
(Skeletal) STERNEBRA(E), 5-6, UNOSSIFIED - VARIATION, 6 ONLY	
VERTEBRAL COLUMN	
(Skeletal) VERTEBRAE, 27 PRESACRAL VERTEBRAE - VARIATION	
Fetal Position: Left 03	Unique Fetal Id.: 3
THORACIC CAVITY	
(Visceral) HEART, MAJOR BLOOD VESSEL, VARIATION - VARIATION, RETROESOPHAGEAL RIGHT SUBCLAVIAN	
RIBS	
(Skeletal) RIB 13, RUDIMENTARY - VARIATION, BILATERAL	
STERNUM	
(Skeletal) STERNEBRA(E), 5-6, UNOSSIFIED - VARIATION	
Fetal Position: Left 04	Unique Fetal Id.: 4
RIBS	
(Skeletal) RIB 13, FULL - VARIATION, LEFT FULL, RIGHT RUDIMENTARY	
VERTEBRAL COLUMN	
(Skeletal) VERTEBRAE, 27 PRESACRAL VERTEBRAE - VARIATION	

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UIC/TRL STUDY NO. 173 DEVELOPMENTAL TOXICITY (SEGMENT II) STUDY OF WR6026 DIHYDROCHLORIDE IN RABBITS

INDIVIDUAL FETAL MORPHOLOGICAL OBSERVATIONS

GROUP 2: 3 MG BASE/KG/DAY

Animal: 724 (CONT.)
Fetal Position: Left 05 Unique Fetal Id.: 5
RIBS (Skeletal) RIB 13, FULL - VARIATION; BILATERAL
VERTEBRAL COLUMN
(Skeletal) VERTEBRAE, 27 PRESACRAL VERTEBRAE - VARIATION
SKULL
(Skeletal) HYOID BODY, UNOSSIFIED - VARIATION
ABDOMEN
(Visceral) URETER(S), RETROCAVAL - VARIATION; RIGHT
Fetal Position: Left 06 * Unique Fetal Id.: 6
RIBS (Skeletal) RIB 13, FULL - VARIATION; LEFT RUDIMENTARY, RIGHT FULL
SKULL
(Skeletal) HYOID BODY, UNOSSIFIED - VARIATION
HINDLIMBS
(Skeletal) TALUS, UNOSSIFIED - VARIATION; BILATERAL
EYES
(External) EYE(S), MACROPHthalmia - MALFORMATION; BILATERAL
Comments: MACROPHthalmia -- BILATERAL NOT CONFIRMED AT SKELETAL EXAMINATION
Fetal Position: Left 07 Unique Fetal Id.: 7
RIBS (Skeletal) RIB 13, RUDIMENTARY - VARIATION; BILATERAL
STERNUM
(Skeletal) STERNEBRA(E), 5-6, UNOSSIFIED - VARIATION; 5 ONLY
HINDLIMBS
(Skeletal) TALUS, UNOSSIFIED - VARIATION; BILATERAL

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INDIVIDUAL FETAL MORPHOLOGICAL OBSERVATIONS

GROUP 2: 3 MG BASE/KG/DAY

Animal: 724 (CONT.)
Fetal Position: Right 01 * Unique Fetal Id.: 8
RIBS
(Skeletal) RIB 13, FULL - VARIATION; BILATERAL

STERNUM
(Skeletal) STERNEBRA(E), 5-6, UNOSSIFIED - VARIATION

VERTEBRAL COLUMN
(Skeletal) VERTEBRAE, 27 PRESACRAL VERTEBRAE - VARIATION

ABDOMEN
(Visceral) URETER(S), RETROCAVAL - VARIATION; RIGHT

COMMENT: COULD NOT CONFIRM EXTERNAL OBSERVATION OF SHORT TAIL; CAUDAL VERTEBRAE NORMAL

Fetal Position: Right 02 Unique Fetal Id.: 9
RIBS
(Skeletal) RIB 13, FULL - VARIATION; RIGHT

STERNUM
(Skeletal) STERNEBRA(E), 5-6, UNOSSIFIED - VARIATION; 6 ONLY
Fetal Position: Right 04 Unique Fetal Id.: 11
RIBS
(Skeletal) RIB 13, FULL - VARIATION; BILATERAL

VERTEBRAL COLUMN
(Skeletal) VERTEBRAE, 27 PRESACRAL VERTEBRAE - VARIATION

Animal: 725
Fetal Position: Left 01 Unique Fetal Id.: 1
STERNUM
(Skeletal) STERNEBRA(E), 5-6, UNOSSIFIED - VARIATION; 5 ONLY

Animal: 726
Fetal Position: Left 02 Unique Fetal Id.: 2
THORACIC CAVITY
(Visceral) HEART, MAJOR BLOOD VESSEL, VARIATION - VARIATION; LEFT
CAROTID ARISES FROM THE BRACHIOCEPHALIC TRUNK

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UIC/TRL STUDY NO. 173 DEVELOPMENTAL TOXICITY (SEGMENT II) STUDY OF WR6026 DIHYDROCHLORIDE IN RABBITS

INDIVIDUAL FETAL MORPHOLOGICAL OBSERVATIONS

GROUP 2: 3 MG BASE/KG/DAY

Animal: 726 (CONT.)	Unique Fetal Id.: 3
Fetal Position: Left 03	
THORACIC CAVITY	
(Visceral) HEART, MAJOR BLOOD VESSEL, VARIATION - VARIATION; LEFT	
CAROTID ARISES FROM THE BRACHIOCEPHALIC TRUNK	
RIBS	
(Skeletal) RIB 13, FULL - VARIATION; BILATERAL	
STERNUM	
(Skeletal) STERNEBRA (E), MALALIGNED, SLIGHT TO MODERATE - VARIATION; 4 AND 5, SLIGHT	
Fetal Position: Right 01	Unique Fetal Id.: 4
RIBS	
(Skeletal) RIB 13, FULL - VARIATION; LEFT RUDIMENTARY (NO ARTICULATING HEAD), RIGHT FULL	
Fetal Position: Right 02	Unique Fetal Id.: 5
STERNUM	
(Skeletal) STERNEBRA (E), MALALIGNED, SLIGHT TO MODERATE - VARIATION; 4, SLIGHT	
Fetal Position: Right 03	Unique Fetal Id.: 6
RIBS	
(Skeletal) RIB 13, RUDIMENTARY - VARIATION; BILATERAL (NO ARTICULATING HEADS)	
STERNUM	
(Skeletal) STERNEBRA (E), MALALIGNED, SLIGHT TO MODERATE - VARIATION; 4, SLIGHT	
STERNEBRA (E), 5-6, UNOSSIFIED - VARIATION; 5 ONLY	
Fetal Position: Right 04	Unique Fetal Id.: 7
RIBS	
(Skeletal) RIB 13, FULL - VARIATION; BILATERAL	

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INDIVIDUAL FETAL MORPHOLOGICAL OBSERVATIONS

GROUP 2: 3 MG BASE/KG/DAY

Animal: 727
Fetal Position: Left 01 Unique Fetal Id.: 1
RIBS
(Skeletal) RIB 13, FULL - VARIATION; BILATERAL

Fetal Position: Left 02 Unique Fetal Id.: 2
RIBS
(Skeletal) RIB 13, RUDIMENTARY - VARIATION; LEFT

Fetal Position: Left 03 Unique Fetal Id.: 3
RIBS
(Skeletal) RIB 13, FULL - VARIATION; BILATERAL

VERTEBRAL COLUMN
(Skeletal) VERTEBRAE, 27 PRESACRAL VERTEBRAE - VARIATION

Fetal Position: Left 04 Unique Fetal Id.: 4
RIBS
(Skeletal) RIB 13, FULL - VARIATION; BILATERAL

Fetal Position: Right 01 Unique Fetal Id.: 5
RIBS
(Skeletal) RIB 13, FULL - VARIATION; BILATERAL

Fetal Position: Right 02 Unique Fetal Id.: 6
RIBS
(Skeletal) RIB 13, RUDIMENTARY - VARIATION; RIGHT

Fetal Position: Right 03 Unique Fetal Id.: 7
RIBS
(Skeletal) RIB 13, FULL - VARIATION; LEFT

Animal: 729
Fetal Position: Left 01 Unique Fetal Id.: 1
VERTEBRAL COLUMN
(Skeletal) VERTEBRAE, 27 PRESACRAL VERTEBRAE - VARIATION

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INDIVIDUAL FETAL MORPHOLOGICAL OBSERVATIONS

GROUP 2: 3 MG BASE/KG/DAY

Animal: 729 (CONT.)		
Fetal Position: Left 02		Unique Fetal Id.: 2
RIBS		
(Skeletal) RIB 13, RUDIMENTARY - VARIATION; BILATERAL		
Fetal Position: Left 03		Unique Fetal Id.: 3
RIBS		
(Skeletal) RIB 13, RUDIMENTARY - VARIATION; LEFT		
STERNUM		
(Skeletal) STERNEBRA(E), 5-6, UNOSSIFIED - VARIATION; 6 ONLY		
Fetal Position: Left 04		Unique Fetal Id.: 4
RIBS		
(Skeletal) RIB 13, FULL - VARIATION; LEFT RUDIMENTARY, RIGHT FULL		
VERTEBRAL COLUMN		
(Skeletal) VERTEBRAE, 27 PRESACRAL VERTEBRAE - VARIATION		
Fetal Position: Right 01		Unique Fetal Id.: 5
RIBS		
(Skeletal) RIB 13, RUDIMENTARY - VARIATION; BILATERAL		
STERNUM		
(Skeletal) STERNEBRA(E), 5-6, UNOSSIFIED - VARIATION; 5 ONLY		
Fetal Position: Right 02		Unique Fetal Id.: 6
RIBS		
(Skeletal) RIB 13, FULL - VARIATION; LEFT FULL, RIGHT RUDIMENTARY		
STERNUM		
(Skeletal) STERNEBRA(E), 5-6, UNOSSIFIED - VARIATION; 5 ONLY		

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INDIVIDUAL FETAL MORPHOLOGICAL OBSERVATIONS

GROUP 2: 3 MG BASE/KG/DAY

Animal: 729 (CONT.)
Fetal Position: Right 03
RIBS (Skeletal) RIB 13, RUDIMENTARY - VARIATION; LEFT Unique Fetal Id.: 7

STERNUM (Skeletal) STERNEBRA(E), 5-6, UNOSSIFIED - VARIATION
Fetal Position: Right 04
RIBS (Skeletal) RIB 13, FULL - VARIATION; LEFT FULL, RIGHT RUDIMENTARY Unique Fetal Id.: 8

STERNUM (Skeletal) STERNEBRA(E), 5-6, UNOSSIFIED - VARIATION; 5 ONLY
Fetal Position: Right 05
RIBS (Skeletal) RIB 13, FULL - VARIATION; BILATERAL Unique Fetal Id.: 9

STERNUM (Skeletal) STERNEBRA(E), 5-6, UNOSSIFIED - VARIATION
Fetal Position: Right 06
RIBS (Skeletal) RIB 13, FULL - VARIATION; BILATERAL Unique Fetal Id.: 10

STERNUM (Skeletal) STERNEBRA(E), 5-6, UNOSSIFIED - VARIATION
Fetal Position: Right 07
RIBS (Skeletal) RIB 13, FULL - VARIATION; BILATERAL Unique Fetal Id.: 11

VERTEBRAL COLUMN
(Skeletal) VERTEBRAE, 27 PRESACRAL VERTEBRAE - VARIATION

EYES (Visceral) AROUND IRIS, HEMORRHAGIC RING - VARIATION; LEFT

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INDIVIDUAL FETAL MORPHOLOGICAL OBSERVATIONS

GROUP 2: 3 MG BASE/KG/DAY

Animal: 730
Fetal Position: Left 02 Unique Fetal Id.: 2
RIBS
(Skeletal) RIB 13, FULL - VARIATION; BILATERAL

VERTEBRAL COLUMN
(Skeletal) VERTEBRAE, 27 PRESACRAL VERTEBRAE - VARIATION

Fetal Position: Left 04 Unique Fetal Id.: 4
RIBS
(Skeletal) RIB 13, FULL - VARIATION; BILATERAL

STERNUM
(Skeletal) STERNEBRA(E), 5-6, UNOSSIFIED - VARIATION; 5 ONLY

VERTEBRAL COLUMN
(Skeletal) VERTEBRAE, 27 PRESACRAL VERTEBRAE - VARIATION

Fetal Position: Left 05 Unique Fetal Id.: 5
RIBS
(Skeletal) RIB 13, FULL - VARIATION; BILATERAL

VERTEBRAL COLUMN
(Skeletal) VERTEBRAE, 27 PRESACRAL VERTEBRAE - VARIATION

Fetal Position: Right 01 Unique Fetal Id.: 6
RIBS
(Skeletal) RIB 13, FULL - VARIATION; BILATERAL

Fetal Position: Right 02 Unique Fetal Id.: 7
STERNUM
(Skeletal) STERNEBRA(E), 5-6, UNOSSIFIED - VARIATION; 5 ONLY

Fetal Position: Right 03 Unique Fetal Id.: 8
RIBS
(Skeletal) RIB 13, FULL - VARIATION; BILATERAL

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INDIVIDUAL FETAL MORPHOLOGICAL OBSERVATIONS

GROUP 2: 3 MG BASE/KG/DAY

Animal: 730 (CONT.)
Fetal Position: Right 04 Unique Fetal Id.: 9
RIBS
(Skeletal) RIB 13, FULL - VARIATION; BILATERAL

Animal: 731
Fetal Position: Left 01 Unique Fetal Id.: 1
RIBS
(Skeletal) RIB 13, FULL - VARIATION; BILATERAL

STERNUM
(Skeletal) STERNEBRA (E), MALALIGNED, SLIGHT TO MODERATE - VARIATION;
4 AND 5, SLIGHT

Fetal Position: Left 02 Unique Fetal Id.: 2
RIBS
(Skeletal) RIB 13, FULL - VARIATION; LEFT FULL, RIGHT RUDIMENTARY

Fetal Position: Left 03 Unique Fetal Id.: 3
RIBS
(Skeletal) RIB 13, RUDIMENTARY - VARIATION; BILATERAL

Fetal Position: Left 04 Unique Fetal Id.: 4
RIBS
(Skeletal) RIB 13, FULL - VARIATION; LEFT FULL, RIGHT RUDIMENTARY

Fetal Position: Left 05 Unique Fetal Id.: 5
RIBS
(Skeletal) RIB 13, FULL - VARIATION; BILATERAL

VERTEBRAL COLUMN
(Skeletal) VERTEBRAE, 27 PRESACRAL VERTEBRAE - VARIATION

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INDIVIDUAL FETAL MORPHOLOGICAL OBSERVATIONS

GROUP 2: 3 MG BASE/KG/DAY

Animal: 731 (CONT.)	Unique Fetal Id.: 6
Fetal Position: Right 01	
RIBS	
(Skeletal) RIB 13, FULL - VARIATION; LEFT FULL, RIGHT RUDIMENTARY	
VERTEBRAL COLUMN	
(Skeletal) VERTEBRAE, 27 PRESACRAL VERTEBRAE - VARIATION	
Fetal Position: Right 02	Unique Fetal Id.: 7
RIBS	
(Skeletal) RIB 13, FULL - VARIATION; BILATERAL	
VERTEBRAL COLUMN	
(Skeletal) VERTEBRAE, 27 PRESACRAL VERTEBRAE - VARIATION	
Fetal Position: Right 03	Unique Fetal Id.: 8
RIBS	
(Skeletal) RIB 13, FULL - VARIATION; BILATERAL	
Fetal Position: Right 04	Unique Fetal Id.: 9
RIBS	
(Skeletal) RIB 13, FULL - VARIATION; BILATERAL	
Animal: 732	
Fetal Position: Left 01	Unique Fetal Id.: 1
THORACIC CAVITY	
(Visceral) HEART, MAJOR BLOOD VESSEL, VARIATION - VARIATION; LEFT CAROTID ARISES FROM BRACHIOCEPHALIC TRUNK	
STERNUM	
(Skeletal) STERNEBRA(E), 5-6, UNOSSIFIED - VARIATION; 5 ONLY	
Fetal Position: Left 02	Unique Fetal Id.: 2
STERNUM	
(Skeletal) STERNEBRA(E), MALALIGNED, SLIGHT TO MODERATE - VARIATION; 3, 4 AND 5, SLIGHT	

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INDIVIDUAL FETAL MORPHOLOGICAL OBSERVATIONS

GROUP 2: 3 MG BASE/KG/DAY

Animal: 732 (CONT.)	Unique Fetal Id.: 3
Fetal Position: Left 03	
RIBS	
(Skeletal) RIB 13, RUDIMENTARY - VARIATION; RIGHT	
STERNUM	
(Skeletal) STERNEBRA (E), MALALIGNED, SLIGHT TO MODERATE - VARIATION; 3 AND 4, SLIGHT	
STERNEBRA (E), 5-6, UNOSSIFIED - VARIATION; 5 ONLY	
Fetal Position: Right 02	Unique Fetal Id.: 6
RIBS	
(Skeletal) RIB 13, FULL - VARIATION; BILATERAL	
Fetal Position: Right 03	Unique Fetal Id.: 7
STERNUM	
(Skeletal) STERNEBRA (E), 5-6, UNOSSIFIED - VARIATION; 5 ONLY	
Fetal Position: Right 05	Unique Fetal Id.: 9
STERNUM	
(Skeletal) STERNEBRA (E), MALALIGNED, SLIGHT TO MODERATE - VARIATION; 4, SLIGHT	
Fetal Position: Right 06	Unique Fetal Id.: 10
RIBS	
(Skeletal) RIB 13, RUDIMENTARY - VARIATION; LEFT	
Fetal Position: Right 07	Unique Fetal Id.: 11
STERNUM	
(Skeletal) STERNEBRA (E), MALALIGNED, SLIGHT TO MODERATE - VARIATION; 3 AND 4, SLIGHT	
Animal: 733	
Fetal Position: Left 01	Unique Fetal Id.: 1
RIBS	
(Skeletal) RIB 13, FULL - VARIATION; BILATERAL	

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INDIVIDUAL FETAL MORPHOLOGICAL OBSERVATIONS

GROUP 2: 3 MG BASE/KG/DAY

Animal: 733 (CONT.)		
Fetal Position: Left 04		Unique Fetal Id.: 4
STERNUM		
(Skeletal) STERNEBRA(E), 5-6, UNOSSIFIED - VARIATION;		5 ONLY
Fetal Position: Left 06		Unique Fetal Id.: 6
RIBS		
(Skeletal) RIB 13, RUDIMENTARY - VARIATION; RIGHT (NO ARTICULATING HEAD)		
Fetal Position: Right 01		Unique Fetal Id.: 7
STERNUM		
(Skeletal) STERNEBRA(E), 5-6, UNOSSIFIED - VARIATION;		5 ONLY
Fetal Position: Right 02		Unique Fetal Id.: 8
STERNUM		
(Skeletal) STERNEBRA(E), 5-6, UNOSSIFIED - VARIATION;		5 ONLY
Fetal Position: Right 03		Unique Fetal Id.: 9
STERNUM		
(Skeletal) STERNEBRA(E), 5-6, UNOSSIFIED - VARIATION;		5 ONLY
Fetal Position: Right 05		Unique Fetal Id.: 11
SKULL		
(Skeletal) HYOID ARCH(ES), BENT - VARIATION; BILATERAL, SLIGHT		
Animal: 734		
Fetal Position: Left 01		Unique Fetal Id.: 1
STERNUM		
(Skeletal) STERNEBRA(E), MALALIGNED, SLIGHT TO MODERATE - VARIATION;		3, 4 AND 5, SLIGHT

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INDIVIDUAL FETAL MORPHOLOGICAL OBSERVATIONS

GROUP 2: 3 MG BASE/KG/DAY

Animal: 734 (CONT.)
Fetal Position: Right 01
RIBS Unique Fetal Id.: 2
(Skeletal) RIB 13, RUDIMENTARY - VARIATION; LEFT

STERNUM
(Skeletal) STERNEBRA(E), 5-6, UNOSSIFIED - VARIATION; 6 ONLY

Animal: 735
Fetal Position: Left 01
STERNUM Unique Fetal Id.: 1
(Skeletal) STERNEBRA(E), 5-6, UNOSSIFIED - VARIATION; 5 ONLY

Fetal Position: Left 02
STERNUM Unique Fetal Id.: 2
(Skeletal) STERNEBRA(E), 5-6, UNOSSIFIED - VARIATION; 5 ONLY

Fetal Position: Right 02
STERNUM Unique Fetal Id.: 7
(Skeletal) STERNEBRA(E), 5-6, UNOSSIFIED - VARIATION; 5 ONLY

Fetal Position: Right 03
RIBS Unique Fetal Id.: 8
(Skeletal) RIB 13, FULL - VARIATION; LEFT FULL, RIGHT RUDIMENTARY

VERTEBRAL COLUMN

(Skeletal) VERTEBRAE, 27 PRESACRAL VERTEBRAE - VARIATION

Fetal Position: Right 04
STERNUM Unique Fetal Id.: 9
(Skeletal) STERNEBRA(E), 5-6, UNOSSIFIED - VARIATION; 5 ONLY

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INDIVIDUAL FETAL MORPHOLOGICAL OBSERVATIONS

GROUP 2: 3 MG BASE/KG/DAY

Animal: 735 (CONT.)	Unique Fetal Id.: 10
Fetal Position: Right 05	
RIBS	
(Skeletal) RIB 13, FULL - VARIATION, RIGHT	
STERNUM	
(Skeletal) STERNEBRA(E), 5-6, UNOSSIFIED - VARIATION, 5 ONLY	
VERTEBRAL COLUMN	
(Skeletal) VERTEBRAE, 27 PRESACRAL VERTEBRAE - VARIATION	
Fetal Position: Right 06	Unique Fetal Id.: 11
STERNUM	
(Skeletal) STERNEBRA(E), MALALIGNED, SLIGHT TO MODERATE - VARIATION, 2, 3 AND 4, SLIGHT	
VERTEBRAL COLUMN	
(Skeletal) VERTEBRAE/RIBS, ANOMALY - MALFORMATION, 2 LEFT ARCHES ASSOCIATED WITH THORACIC CENTRUM 7--EACH ARCH HAS RIB--RIBS ARE FUSED AT PROXIMAL END, EXTRA RIGHT ARCH BETWEEN RIGHT THORACIC ARCHES 4 AND 5--RIB ASSOCIATED WITH THIS ARCH, 13TH FULL RIB, BILATERAL	
SKULL	
(Skeletal) HYOID BODY, UNOSSIFIED - VARIATION	
HINDLIMBS	
(Skeletal) TALUS, UNOSSIFIED - VARIATION, BILATERAL	
Animal: 736	Unique Fetal Id.: 1
Fetal Position: Left 01	
RIBS	
(Skeletal) RIB 13, FULL - VARIATION, BILATERAL	
VERTEBRAL COLUMN	
(Skeletal) VERTEBRAE, 27 PRESACRAL VERTEBRAE - VARIATION	

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INDIVIDUAL FETAL MORPHOLOGICAL OBSERVATIONS

GROUP 2: 3 MG BASE/KG/DAY

Animal: 736 (CONT.)
Fetal Position: Left 02 Unique Fetal Id.: 2
RIBS
(Skeletal) RIB 13, FULL - VARIATION; RIGHT

Fetal Position: Right 01 Unique Fetal Id.: 3
RIBS
(Skeletal) RIB 13, FULL - VARIATION; BILATERAL

STERNUM
(Skeletal) STERNEBRA(E), 5-6, UNOSSIFIED - VARIATION; 6 ONLY

Fetal Position: Right 02 Unique Fetal Id.: 4
STERNUM
(Skeletal) STERNEBRA(E), 5-6, UNOSSIFIED - VARIATION; 6 ONLY

Fetal Position: Right 03 Unique Fetal Id.: 5
RIBS
(Skeletal) RIB 13, RUDIMENTARY - VARIATION; LEFT (NO ARTICULATING HEAD)

Fetal Position: Right 05 Unique Fetal Id.: 7
RIBS
(Skeletal) RIB 13, RUDIMENTARY - VARIATION; LEFT

STERNUM
(Skeletal) STERNEBRA(E), 5-6, UNOSSIFIED - VARIATION; 6 ONLY

Fetal Position: Right 06 Unique Fetal Id.: 8
SKULL
(Skeletal) HYOID BODY, UNOSSIFIED - VARIATION
HYOID ARCH(ES), UNOSSIFIED - VARIATION; BILATERAL

Note: For Dam 736, Fetus 5, a visceral examination of the thoracic cavity and organs was not performed.

APPENDIX D

UIC/TRL STUDY NO. 173 DEVELOPMENTAL TOXICITY (SEGMENT II) STUDY OF WR6026 DIHYDROCHLORIDE IN RABBITS

INDIVIDUAL FETAL MORPHOLOGICAL OBSERVATIONS

GROUP 2: 3 MG BASE/KG/DAY

Animal: 737		Unique Fetal Id.: 1
Fetal Position: Left 01		
RIBS		
(Skeletal) RIB 13, FULL - VARIATION; LEFT FULL, RIGHT RUDIMENTARY		
7TH CERVICAL RIB, PRESENT - VARIATION; RIGHT		
STERNUM		
(Skeletal) STERNEBRA(E), 5-6, UNOSSIFIED - VARIATION; 5 ONLY		
Fetal Position: Left 02		Unique Fetal Id.: 2
RIBS		
(Skeletal) RIB 13, FULL - VARIATION; BILATERAL		
VERTEBRAL COLUMN		
(Skeletal) VERTEBRAE, 27 PRESACRAL VERTEBRAE - VARIATION		
Fetal Position: Left 03		Unique Fetal Id.: 3
RIBS		
(Skeletal) RIB 13, FULL - VARIATION; LEFT FULL, RIGHT RUDIMENTARY		
Fetal Position: Left 04		Unique Fetal Id.: 4
RIBS		
(Skeletal) RIB 13, FULL - VARIATION; BILATERAL		
SKULL		
(Skeletal) HYOID ARCH(ES), BENT - VARIATION; LEFT MODERATE, RIGHT SLIGHT		
Fetal Position: Right 01		Unique Fetal Id.: 5
RIBS		
(Skeletal) RIB 13, FULL - VARIATION; LEFT FULL, RIGHT RUDIMENTARY		
STERNUM		
(Skeletal) STERNEBRA(E), 5-6, UNOSSIFIED - VARIATION; 5 ONLY		
Fetal Position: Right 02		Unique Fetal Id.: 6
STERNUM		
(Skeletal) STERNEBRA(E), 5-6, UNOSSIFIED - VARIATION; 5 ONLY		

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UIC/TRL STUDY NO. 173 DEVELOPMENTAL TOXICITY (SEGMENT II) STUDY OF WR6026 DIHYDROCHLORIDE IN RABBITS
INDIVIDUAL FETAL MORPHOLOGICAL OBSERVATIONS

GROUP 2: 3 MG BASE/KG/DAY

Animal: 737 (CONT.)		
Fetal Position: Right 04		Unique Fetal Id.: 8
RIBS		
(Skeletal) RIB 13, FULL - VARIATION; LEFT FULL, RIGHT RUDIMENTARY		
Animal: 738		
Fetal Position: Left 01		Unique Fetal Id.: 1
RIBS		
(Skeletal) RIB 13, FULL - VARIATION; BILATERAL		
Fetal Position: Left 04		Unique Fetal Id.: 4
STERNUM		
(Skeletal) STERNEBRA(E), 5-6, UNOSSIFIED - VARIATION; 6 ONLY		
Fetal Position: Left 05		Unique Fetal Id.: 5
STERNUM		
(Skeletal) STERNEBRA(E), 5-6, UNOSSIFIED - VARIATION; 5 ONLY		
Fetal Position: Left 06		Unique Fetal Id.: 6
RIBS		
(Skeletal) RIB 13, RUDIMENTARY - VARIATION; LEFT (NO ARTICULATING HEAD)		
Fetal Position: Left 07		
Late Resorption: Crown-Rump Length: 31 mm		
Fetal Position: Right 01		Unique Fetal Id.: 8
STERNUM		
(Skeletal) STERNEBRA(E), 5-6, UNOSSIFIED - VARIATION; 5 ONLY		
Animal: 739		
Fetal Position: Left 01		Unique Fetal Id.: 1
RIBS		
(Skeletal) RIB 13, FULL - VARIATION; BILATERAL		
Fetal Position: Left 02		Unique Fetal Id.: 2
RIBS		
(Skeletal) 7TH CERVICAL RIB, PRESENT - VARIATION; RIGHT		

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UIC/TRL STUDY NO. 173 DEVELOPMENTAL TOXICITY (SEGMENT II) STUDY OF WR6026 DIHYDROCHLORIDE IN RABBITS

INDIVIDUAL FETAL MORPHOLOGICAL OBSERVATIONS

GROUP 2: 3 MG BASE/KG/DAY

Animal: 739 (CONT.)		
Fetal Position: Left 03		Unique Fetal Id.: 3
RIBS		
(Skeletal) RIB 13, FULL - VARIATION; BILATERAL		
Fetal Position: Left 05		Unique Fetal Id.: 5
RIBS		
(Skeletal) RIB 13, FULL - VARIATION; BILATERAL		
VERTEBRAL COLUMN		
(Skeletal) VERTEBRAE, 27 PRESACRAL VERTEBRAE - VARIATION		
Fetal Position: Left 06		Unique Fetal Id.: 6
RIBS		
(Skeletal) RIB 13, FULL - VARIATION; BILATERAL		
VERTEBRAL COLUMN		
(Skeletal) VERTEBRAE, 27 PRESACRAL VERTEBRAE - VARIATION		
Fetal Position: Right 01		Unique Fetal Id.: 7
RIBS		
(Skeletal) RIB 13, FULL - VARIATION; BILATERAL		
VERTEBRAL COLUMN		
(Skeletal) VERTEBRAE, 27 PRESACRAL VERTEBRAE - VARIATION		
Fetal Position: Right 02		Unique Fetal Id.: 8
RIBS		
(Skeletal) RIB 13, FULL - VARIATION; BILATERAL		

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UIC/TRL STUDY NO. 173 DEVELOPMENTAL TOXICITY (SEGMENT II) STUDY OF WR6026 DIHYDROCHLORIDE IN RABBITS

INDIVIDUAL FETAL MORPHOLOGICAL OBSERVATIONS

GROUP 3: 7 MG BASE/KG/DAY

Animal: 741		
Fetal Position: Left 01		Unique Fetal Id.: 1
RIBS		
(Skeletal) RIB 13, FULL - VARIATION; BILATERAL		
VERTEBRAL COLUMN		
(Skeletal) VERTEBRAE, 27 PRESACRAL VERTEBRAE - VARIATION		
Fetal Position: Left 02		Unique Fetal Id.: 2
RIBS		
(Skeletal) RIB 13, FULL - VARIATION; LEFT RUDIMENTARY, RIGHT FULL		
VERTEBRAL COLUMN		
(Skeletal) VERTEBRAE, 27 PRESACRAL VERTEBRAE - VARIATION		
Fetal Position: Left 03		Unique Fetal Id.: 3
RIBS		
(Skeletal) RIB 13, FULL - VARIATION; BILATERAL		
VERTEBRAL COLUMN		
(Skeletal) VERTEBRAE, 27 PRESACRAL VERTEBRAE - VARIATION		
Fetal Position: Right 01		Unique Fetal Id.: 4
RIBS		
(Skeletal) RIB 13, FULL - VARIATION; BILATERAL		
VERTEBRAL COLUMN		
(Skeletal) VERTEBRAE, 27 PRESACRAL VERTEBRAE - VARIATION		
Fetal Position: Right 02		Unique Fetal Id.: 5
RIBS		
(Skeletal) RIB 13, FULL - VARIATION; BILATERAL		
VERTEBRAL COLUMN		
(Skeletal) VERTEBRAE, 27 PRESACRAL VERTEBRAE - VARIATION		

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INDIVIDUAL FETAL MORPHOLOGICAL OBSERVATIONS

GROUP 3: 7 MG BASE/KG/DAY

Animal: 741 (CONT.)		Unique Fetal Id.: 6
Fetal Position: Right 03		
RIBS		
(Skeletal) RIB 13, FULL - VARIATION; BILATERAL		
VERTEBRAL COLUMN		
(Skeletal) VERTEBRAE, 27 PRESACRAL VERTEBRAE - VARIATION		
Fetal Position: Right 04		Unique Fetal Id.: 7
RIBS		
(Skeletal) RIB 13, FULL - VARIATION; BILATERAL		
VERTEBRAL COLUMN		
(Skeletal) VERTEBRAE, 27 PRESACRAL VERTEBRAE - VARIATION		
Fetal Position: Right 05		Unique Fetal Id.: 8
RIBS		
(Skeletal) RIB 13, FULL - VARIATION; BILATERAL		
STERNUM		
(Skeletal) STERNEBRA(E), MALALIGNED, SLIGHT TO MODERATE - VARIATION; 4 AND 5, SLIGHT		
VERTEBRAL COLUMN		
(Skeletal) VERTEBRAE, 27 PRESACRAL VERTEBRAE - VARIATION		
Fetal Position: Right 07		Unique Fetal Id.: 10
RIBS		
(Skeletal) RIB 13, FULL - VARIATION; BILATERAL		
Animal: 742		
Fetal Position: Left 01		Unique Fetal Id.: 1
RIBS		
(Skeletal) RIB 13, FULL - VARIATION; BILATERAL		

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UIC/TRL STUDY NO. 173 DEVELOPMENTAL TOXICITY (SEGMENT II) STUDY OF WR6026 DIHYDROCHLORIDE IN RABBITS

INDIVIDUAL FETAL MORPHOLOGICAL OBSERVATIONS

GROUP 3: 7 MG BASE/KG/DAY

Animal: 742 (CONT.)
Fetal Position: Left 02
RIBS Unique Fetal Id.: 2

(Skeletal) RIB 13, FULL - VARIATION; BILATERAL

VERTEBRAL COLUMN

(Skeletal) VERTEBRAE, 27 PRESACRAL VERTEBRAE - VARIATION

Fetal Position: Left 03
RIBS Unique Fetal Id.: 3

(Skeletal) RIB 13, FULL - VARIATION; BILATERAL

Fetal Position: Right 01
RIBS Unique Fetal Id.: 4

(Skeletal) RIB 13, FULL - VARIATION; BILATERAL

VERTEBRAL COLUMN

(Skeletal) VERTEBRAE, 27 PRESACRAL VERTEBRAE - VARIATION

Fetal Position: Right 02
RIBS Unique Fetal Id.: 5

(Skeletal) RIB 13, FULL - VARIATION; BILATERAL

VERTEBRAL COLUMN

(Skeletal) VERTEBRAE, 27 PRESACRAL VERTEBRAE - VARIATION

Fetal Position: Right 03
Late Resorption: Crown/Rump Length: 40 mm

Fetal Position: Right 04
RIBS Unique Fetal Id.: 7

(Skeletal) RIB 13, FULL - VARIATION; BILATERAL

Fetal Position: Right 05
RIBS Unique Fetal Id.: 8

(Skeletal) RIB 13, FULL - VARIATION; BILATERAL

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UIC/TRL STUDY NO. 173 DEVELOPMENTAL TOXICITY (SEGMENT II) STUDY OF WR6026 DIHYDROCHLORIDE IN RABBITS

INDIVIDUAL FETAL MORPHOLOGICAL OBSERVATIONS

GROUP 3: 7 MG BASE/KG/DAY

Animal: 743		Unique Fetal Id.: 1
Fetal Position: Left 01		
STERNUM		
(Skeletal) STERNEBRA(E), 5-6, UNOSSIFIED - VARIATION; 5 ONLY		
Fetal Position: Left 02		Unique Fetal Id.: 2
RIBS		
(Skeletal) RIB 13, FULL - VARIATION; BILATERAL		
Fetal Position: Left 04		Unique Fetal Id.: 4
RIBS		
(Skeletal) RIB 13, RUDIMENTARY - VARIATION; BILATERAL		
Fetal Position: Right 02		Unique Fetal Id.: 6
STERNUM		
(Skeletal) STERNEBRA(E), 5-6, UNOSSIFIED - VARIATION; 5 ONLY		
Fetal Position: Right 03		Unique Fetal Id.: 7
RIBS		
(Skeletal) RIB 13, RUDIMENTARY - VARIATION; BILATERAL		
STERNUM		
(Skeletal) STERNEBRA(E), MALALIGNED, SLIGHT TO MODERATE - VARIATION; 2, 3 AND 4, SLIGHT STERNEBRA(E), 5-6, UNOSSIFIED - VARIATION; 5 ONLY		
VERTEBRAL COLUMN		
(Skeletal) VERTEBRAE, 27 PRESACRAL VERTEBRAE - VARIATION		
Fetal Position: Right 06		Unique Fetal Id.: 10
RIBS		
(Skeletal) RIB 13, RUDIMENTARY - VARIATION; RIGHT		

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UIC/TRL STUDY NO. 173 DEVELOPMENTAL TOXICITY (SEGMENT II) STUDY OF WR6026 DIHYDROCHLORIDE IN RABBITS

INDIVIDUAL FETAL MORPHOLOGICAL OBSERVATIONS

GROUP 3: 7 MG BASE/KG/DAY

Animal: 744
 Fetal Position: Left 01 Unique Fetal Id.: 1
 RIBS
 (Skeletal) RIB 13, FULL - VARIATION; BILATERAL

VERTEBRAL COLUMN
 (Skeletal) VERTEBRAE, 27 PRESACRAL VERTEBRAE - VARIATION

Fetal Position: Left 02 Unique Fetal Id.: 2
 RIBS
 (Skeletal) RIB 13, FULL - VARIATION; BILATERAL

STERNUM
 (Skeletal) STERNEBRA(E), MALALIGNED, SLIGHT TO MODERATE - VARIATION; 4 AND 5, SLIGHT

Fetal Position: Left 03 Unique Fetal Id.: 3
 RIBS
 (Skeletal) RIB 13, FULL - VARIATION; BILATERAL

VERTEBRAL COLUMN
 (Skeletal) VERTEBRAE, 27 PRESACRAL VERTEBRAE - VARIATION

Fetal Position: Left 04 Unique Fetal Id.: 4
 RIBS
 (Skeletal) RIB 13, FULL - VARIATION; LEFT RUDIMENTARY, RIGHT FULL

VERTEBRAL COLUMN
 (Skeletal) VERTEBRAE, 27 PRESACRAL VERTEBRAE - VARIATION

Fetal Position: Left 05 Unique Fetal Id.: 5
 RIBS
 (Skeletal) RIB 13, FULL - VARIATION; BILATERAL

STERNUM
 (Skeletal) STERNEBRA(E), 5-6, UNOSSIFIED - VARIATION

VERTEBRAL COLUMN
 (Skeletal) VERTEBRAE, 27 PRESACRAL VERTEBRAE - VARIATION

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UIC/TRL STUDY NO. 173 DEVELOPMENTAL TOXICITY (SEGMENT II) STUDY OF WR6026 DIHYDROCHLORIDE IN RABBITS

INDIVIDUAL FETAL MORPHOLOGICAL OBSERVATIONS

GROUP 3: 7 MG BASE/KG/DAY

Animal: 744 (CONT.)	Unique Fetal Id.: 6
Fetal Position: Left 06	
RIBS	
(Skeletal) RIB 13, FULL - VARIATION; BILATERAL	
VERTEBRAL COLUMN	
(Skeletal) VERTEBRAE, 27 PRESACRAL VERTEBRAE - VARIATION	
SKULL	
(Skeletal) SKULL, ANOMALY - MALFORMATION; INTERPARIETAL, SMALL IN SIZE	
Fetal Position: Right 01	Unique Fetal Id.: 7
RIBS	
(Skeletal) RIB 13, FULL - VARIATION; BILATERAL	
Fetal Position: Right 02	Unique Fetal Id.: 8
STERNUM	
(Skeletal) STERNEBRA(E), 5-6, UNOSSIFIED - VARIATION	
Fetal Position: Right 03	Unique Fetal Id.: 9
RIBS	
(Skeletal) RIB 13, FULL - VARIATION; BILATERAL	
VERTEBRAL COLUMN	
(Skeletal) VERTEBRAE, 27 PRESACRAL VERTEBRAE - VARIATION	
Animal: 745	Unique Fetal Id.: 1
Fetal Position: Left 01	
STERNUM	
(Skeletal) STERNEBRA(E), 5-6, UNOSSIFIED - VARIATION; 5 ONLY	
Fetal Position: Left 02	Unique Fetal Id.: 2
RIBS	
(Skeletal) RIB 13, RUDIMENTARY - VARIATION; LEFT	
STERNUM	
(Skeletal) STERNEBRA(E), 5-6, UNOSSIFIED - VARIATION; 5 ONLY	

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UIC/TRL STUDY NO. 173 DEVELOPMENTAL TOXICITY (SEGMENT II) STUDY OF WR6026 DIHYDROCHLORIDE IN RABBITS

INDIVIDUAL FETAL MORPHOLOGICAL OBSERVATIONS

GROUP 3: 7 MG BASE/KG/DAY

Animal: 745 (CONT.)		
Fetal Position: Left 03		Unique Fetal Id.: 3
STERNUM		
(Skeletal) STERNEBRA(E), 5-6, UNOSSIFIED - VARIATION;		5 ONLY
Fetal Position: Left 04		Unique Fetal Id.: 4
STERNUM		
(Skeletal) STERNEBRA(E), 5-6, UNOSSIFIED - VARIATION;		5 ONLY
Fetal Position: Left 05		Unique Fetal Id.: 5
STERNUM		
(Skeletal) STERNEBRA(E), 5-6, UNOSSIFIED - VARIATION;		5 ONLY
Fetal Position: Left 06		Unique Fetal Id.: 6
RIBS		
(Skeletal) RIB 13, FULL - VARIATION; LEFT FULL, RIGHT RUDIMENTARY		
Fetal Position: Right 01		Unique Fetal Id.: 7
STERNUM		
(Skeletal) STERNEBRA(E), 5-6, UNOSSIFIED - VARIATION;		5 ONLY
VERTEBRAL COLUMN		
(Skeletal) VERTEBRAE, 27 PRESACRAL VERTEBRAE - VARIATION		
VERTEBRAE/RIBS, ANOMALY - MALFORMATION; LEFT THORACIC		
ARCHES 5 AND 6 FUSED, LEFT RIBS 5 AND 6 FUSED PROXIMAL END		
Fetal Position: Right 02		Unique Fetal Id.: 8
RIBS		
(Skeletal) RIB 13, RUDIMENTARY - VARIATION; BILATERAL		
Fetal Position: Right 03		Unique Fetal Id.: 9
RIBS		
(Skeletal) RIB 13, FULL - VARIATION; BILATERAL		
STERNUM		
(Skeletal) STERNEBRA(E), MALALIGNED, SLIGHT TO MODERATE - VARIATION; 4, SLIGHT		
STERNEBRA(E), 5-6, UNOSSIFIED - VARIATION; 5 ONLY		

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UIC/TRL STUDY NO. 173 DEVELOPMENTAL TOXICITY (SEGMENT II) STUDY OF WR6026 DIHYDROCHLORIDE IN RABBITS

INDIVIDUAL FETAL MORPHOLOGICAL OBSERVATIONS

GROUP 3: 7 MG BASE/KG/DAY

Animal: 745 (CONT.)		Unique Fetal Id.: 10
Fetal Position: Right 04		
RIBS		
(Skeletal) RIB 13, FULL - VARIATION; RIGHT		
Fetal Position: Right 05		Unique Fetal Id.: 11
RIBS		
(Skeletal) RIB 13, FULL - VARIATION; LEFT RUDIMENTARY, RIGHT FULL		
STERNUM		
(Skeletal) STERNEBRA(E), 5-6, UNOSSIFIED - VARIATION; 5 ONLY		
Fetal Position: Right 06		Unique Fetal Id.: 12
RIBS		
(Skeletal) RIB 13, FULL - VARIATION; BILATERAL		
STERNUM		
(Skeletal) STERNEBRA(E), 5-6, UNOSSIFIED - VARIATION; 5 ONLY		
Animal: 746		
Fetal Position: Left 01		Unique Fetal Id.: 1
RIBS		
(Skeletal) RIB 13, FULL - VARIATION; BILATERAL		
VERTEBRAL COLUMN		
(Skeletal) VERTEBRAE, 27 PRESACRAL VERTEBRAE - VARIATION		
Fetal Position: Left 02		Unique Fetal Id.: 2
RIBS		
(Skeletal) RIB 13, RUDIMENTARY - VARIATION; RIGHT		
STERNUM		
(Skeletal) STERNEBRA(E), 5-6, UNOSSIFIED - VARIATION; 5 ONLY		
Fetal Position: Left 03		Unique Fetal Id.: 3
STERNUM		
(Skeletal) STERNEBRA(E), 5-6, UNOSSIFIED - VARIATION; 5 ONLY		

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UIC/TRL STUDY NO. 173 DEVELOPMENTAL TOXICITY (SEGMENT II) STUDY OF WR6026 DIHYDROCHLORIDE IN RABBITS

INDIVIDUAL FETAL MORPHOLOGICAL OBSERVATIONS

GROUP 3: 7 MG BASE/KG/DAY

Animal: 746 (CONT.)	Unique Fetal Id.: 4
Fetal Position: Left 04	
RIBS	
(Skeletal) RIB 13, FULL - VARIATION; BILATERAL	
STERNUM	
(Skeletal) STERNEBRA(E), MALALIGNED, SLIGHT TO MODERATE - VARIATION; 2-5, SLIGHT	
VERTEBRAL COLUMN	
(Skeletal) VERTEBRAE, 27 PRESACRAL VERTEBRAE - VARIATION	
SKULL	
(Skeletal) HYOID BODY, UNOSSIFIED - VARIATION	
Fetal Position: Left 05	Unique Fetal Id.: 5
STERNUM	
(Skeletal) STERNEBRA(E), MALALIGNED, SLIGHT TO MODERATE - VARIATION; 2, 3 AND 4, SLIGHT	
STERNEBRA(E), 5-6, UNOSSIFIED - VARIATION; 5 ONLY	
Fetal Position: Right 01	Unique Fetal Id.: 6
RIBS	
(Skeletal) RIB 13, RUDIMENTARY - VARIATION; LEFT	
Fetal Position: Right 02	Unique Fetal Id.: 7
RIBS	
(Skeletal) 7TH CERVICAL RIB, PRESENT - VARIATION; RIGHT	
STERNUM	
(Skeletal) STERNEBRA(E), 5-6, UNOSSIFIED - VARIATION; 5 ONLY	
Animal: 747	
Fetal Position: Left 01	Unique Fetal Id.: 1
RIBS	
(Skeletal) RIB 13, FULL - VARIATION; BILATERAL	
VERTEBRAL COLUMN	
(Skeletal) VERTEBRAE, 27 PRESACRAL VERTEBRAE - VARIATION	

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INDIVIDUAL FETAL MORPHOLOGICAL OBSERVATIONS

GROUP 3: 7 MG BASE/KG/DAY

Animal: 747 (CONT.)

Fetal Position: Right 01
RIBS

Unique Fetal Id.: 2

(Skeletal) RIB 13, FULL - VARIATION; BILATERAL

Fetal Position: Right 02
RIBS

Unique Fetal Id.: 3

(Skeletal) RIB 13, FULL - VARIATION; LEFT RUDIMENTARY, RIGHT FULL

VERTEBRAL COLUMN

(Skeletal) VERTEBRAE, 27 PRESACRAL VERTEBRAE - VARIATION

Fetal Position: Right 03
RIBS

Unique Fetal Id.: 4

(Skeletal) RIB 13, FULL - VARIATION; LEFT FULL, RIGHT RUDIMENTARY (NO ARTICULATING HEADS)

Fetal Position: Right 04
STERNUM

Unique Fetal Id.: 5

(Skeletal) STERNEBRA(E), MALALIGNED, SLIGHT TO MODERATE - VARIATION; 5, SLIGHT

Fetal Position: Right 05
THORACIC CAVITY
(Visceral)

Unique Fetal Id.: 6

HEART, MAJOR BLOOD VESSEL, VARIATION - VARIATION; LEFT CAROTID ARISING FROM BRACHIOCEPHALIC TRUNK

Fetal Position: Right 06
RIBS

Unique Fetal Id.: 7

(Skeletal) RIB 13, FULL - VARIATION; BILATERAL

Animal: 748

Fetal Position: Left 01
STERNUM

Unique Fetal Id.: 1

(Skeletal) STERNEBRA(E), MALALIGNED, SLIGHT TO MODERATE - VARIATION; 2-5, SLIGHT

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INDIVIDUAL FETAL MORPHOLOGICAL OBSERVATIONS

GROUP 3: 7 MG BASE/KG/DAY

Animal: 748 (CONT.)
Fetal Position: Left 03
RIBS Unique Fetal Id.: 3

(Skeletal) RIB 13, RUDIMENTARY - VARIATION; LEFT

Fetal Position: Right 01
RIBS Unique Fetal Id.: 4

(Skeletal) RIB 13, RUDIMENTARY - VARIATION; LEFT

Fetal Position: Right 03
RIBS Unique Fetal Id.: 6

(Skeletal) RIB 13, RUDIMENTARY - VARIATION; RIGHT

Fetal Position: Right 05
RIBS Unique Fetal Id.: 8

(Skeletal) RIB 13, FULL - VARIATION; BILATERAL

Animal: 749
Fetal Position: Left 01
THORACIC CAVITY Unique Fetal Id.: 1
(Visceral) HEART, MAJOR BLOOD VESSEL, VARIATION - VARIATION; LEFT
CAROTID ARISES FROM THE BRACHIOCEPHALIC TRUNK

RIBS
(Skeletal) RIB 13, FULL - VARIATION; LEFT FULL, RIGHT RUDIMENTARY

Fetal Position: Left 03
RIBS Unique Fetal Id.: 3

(Skeletal) RIB 13, RUDIMENTARY - VARIATION; RIGHT

Note: For Dam 748, Fetuses 4 and 6, a visceral examination of the thoracic cavity and organs was not performed.

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UIC/TRL STUDY NO. 173 DEVELOPMENTAL TOXICITY (SEGMENT II) STUDY OF WR6026 DIHYDROCHLORIDE IN RABBITS

INDIVIDUAL FETAL MORPHOLOGICAL OBSERVATIONS

GROUP 3: 7 MG BASE/KG/DAY

Animal: 749 (CONT.)	Unique Fetal Id.: 4
Fetal Position: Left 04	
RIBS	
(Skeletal) RIB 13, FULL - VARIATION; BILATERAL	
STERNUM	
(Skeletal) STERNEBRA(E), 5-6, UNOSSIFIED - VARIATION; 6 ONLY	
ABDOMEN	
(Visceral) GALL BLADDER, VARIATION - VARIATION; SMALL	
Fetal Position: Left 05	Unique Fetal Id.: 5
THORACIC CAVITY	
(Visceral) HEART, MAJOR BLOOD VESSEL, VARIATION - VARIATION; LEFT	
CAROTID ARISES FROM THE BRACHIOCEPHALIC TRUNK	
RIBS	
(Skeletal) RIB 13, RUDIMENTARY - VARIATION; LEFT	
Fetal Position: Right 02	Unique Fetal Id.: 7
THORACIC CAVITY	
(Visceral) HEART, MAJOR BLOOD VESSEL, VARIATION - VARIATION; LEFT	
CAROTID ARISES FROM THE BRACHIOCEPHALIC TRUNK	
RIBS	
(Skeletal) RIB 13, FULL - VARIATION; BILATERAL	
Fetal Position: Right 03	Unique Fetal Id.: 8
THORACIC CAVITY	
(Visceral) HEART, MAJOR BLOOD VESSEL, VARIATION - VARIATION; LEFT	
CAROTID ARISES FROM THE BRACHIOCEPHALIC TRUNK	
RIBS	
(Skeletal) RIB 13, FULL - VARIATION; BILATERAL	

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INDIVIDUAL FETAL MORPHOLOGICAL OBSERVATIONS

GROUP 3: 7 MG BASE/KG/DAY

Animal: 749 (CONT.)
Fetal Position: Right 04
RIBS
(Skeletal) RIB 13, FULL - VARIATION; BILATERAL
Unique Fetal Id.: 9

STERNUM
(Skeletal) STERNEBRA(E), 5-6, UNOSSIFIED - VARIATION; 6 ONLY

Animal: 750
Fetal Position: Left 01
RIBS
(Skeletal) RIB 13, FULL - VARIATION; BILATERAL
Unique Fetal Id.: 1

VERTEBRAL COLUMN
(Skeletal) VERTEBRAE, 27 PRESACRAL VERTEBRAE - VARIATION

Fetal Position: Left 02
Late Resorption: Crown-Rump Length: 33 mm

Fetal Position: Left 03
RIBS
(Skeletal) RIB 13, RUDIMENTARY - VARIATION; BILATERAL (LEFT--NO ARTICULATING HEAD)
Unique Fetal Id.: 3

Fetal Position: Right 03
RIBS
(Skeletal) RIB 13, RUDIMENTARY - VARIATION; LEFT
Unique Fetal Id.: 6

SKULL
(Skeletal) HYOID ARCH(ES), BENT - VARIATION; LEFT SLIGHT, RIGHT MODERATE

Fetal Position: Right 04
Late Resorption: Crown-Rump Length: 25 mm

Fetal Position: Right 05
VERTEBRAL COLUMN
(Skeletal) VERTEBRAE, 27 PRESACRAL VERTEBRAE - VARIATION
Unique Fetal Id.: 8

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INDIVIDUAL FETAL MORPHOLOGICAL OBSERVATIONS

GROUP 3: 7 MG BASE/KG/DAY

Animal: 750 (CONT.)		
Fetal Position: Right 06		
Late Resorption: Crown-Rump Length: 29 mm		
Fetal Position: Right 07	Unique Fetal Id.: 10	
STERNUM		
(Skeletal) STERNEBRA(E), 5-6, UNOSSIFIED - VARIATION; 6 ONLY		
Animal: 751		
Fetal Position: Left 01	Unique Fetal Id.: 1	
RIBS		
(Skeletal) RIB 13, FULL - VARIATION; BILATERAL		
VERTEBRAL COLUMN		
(Skeletal) VERTEBRAE, 27 PRESACRAL VERTEBRAE - VARIATION		
Fetal Position: Left 02	Unique Fetal Id.: 2	
RIBS		
(Skeletal) RIB 13, FULL - VARIATION; RIGHT		
Fetal Position: Left 03	Unique Fetal Id.: 3	
STERNUM		
(Skeletal) STERNEBRA(E), MALALIGNED, SLIGHT TO MODERATE - VARIATION; 3, 4 AND 5		
Fetal Position: Left 04	Unique Fetal Id.: 4	
RIBS		
(Skeletal) RIB 13, FULL - VARIATION; BILATERAL		
Fetal Position: Right 02	Unique Fetal Id.: 6	
RIBS		
(Skeletal) RIB 13, FULL - VARIATION; BILATERAL		
STERNUM		
(Skeletal) STERNEBRA(E), 5-6, UNOSSIFIED - VARIATION; 5 ONLY		

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INDIVIDUAL FETAL MORPHOLOGICAL OBSERVATIONS

GROUP 3: 7 MG BASE/KG/DAY

Animal: 751 (CONT.)
 Fetal Position: Right 03
 RIBS Unique Fetal Id.: 7

(Skeletal) RIB 13, FULL - VARIATION, BILATERAL

Fetal Position: Right 04
 RIBS Unique Fetal Id.: 8

(Skeletal) RIB 13, FULL - VARIATION, BILATERAL

STERNUM

(Skeletal) STERNEBRA(E), 5-6, UNOSSIFIED - VARIATION; 6 ONLY

VERTEBRAL COLUMN

(Skeletal) VERTEBRAE, 27 PRESACRAL VERTEBRAE - VARIATION

Animal: 752

Fetal Position: Left 01
 THORACIC CAVITY Unique Fetal Id.: 1
 (Visceral) HEART, MAJOR BLOOD VESSEL, VARIATION - VARIATION; LEFT
 SUBCLAVIAN ARISES FROM BRACHIOCEPHALIC TRUNK

RIBS

(Skeletal) RIB 13, FULL - VARIATION; BILATERAL

VERTEBRAL COLUMN

(Skeletal) VERTEBRAE, 27 PRESACRAL VERTEBRAE - VARIATION

Fetal Position: Left 02

Late Resorption: Crown/Rump Length: 85 mm

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INDIVIDUAL FETAL MORPHOLOGICAL OBSERVATIONS

GROUP 3: 7 MG BASE/KG/DAY

Animal: 752 (CONT.)	Unique Fetal Id.: 3
Fetal Position: Left 03	
THORACIC CAVITY	
(Visceral) HEART, MAJOR BLOOD VESSEL, VARIATION - VARIATION; LEFT	
SUBCLAVIAN ARISES FROM BRACHIOCEPHALIC TRUNK	
RIBS	
(Skeletal) RIB 13, RUDIMENTARY - VARIATION; LEFT (NO ARTICULATING HEAD)	
STERNUM	
(Skeletal) STERNEBRA(E), 5-6, UNOSSIFIED - VARIATION; 5 ONLY	
Fetal Position: Left 04	Unique Fetal Id.: 4
RIBS	
(Skeletal) RIB 13, RUDIMENTARY - VARIATION; BILATERAL	
STERNUM	
(Skeletal) STERNEBRA(E), MALALIGNED, SLIGHT TO MODERATE - VARIATION; 4 AND 5, SLIGHT	
Fetal Position: Left 05	Unique Fetal Id.: 5
RIBS	
(Skeletal) RIB 13, FULL - VARIATION; BILATERAL	
STERNUM	
(Skeletal) STERNEBRA(E), 5-6, UNOSSIFIED - VARIATION	
VERTEBRAL COLUMN	
(Skeletal) VERTEBRAE, 27 PRESACRAL VERTEBRAE - VARIATION	
ABDOMEN	
(Visceral) SPLEEN, SMALL IN SIZE - VARIATION	

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DEVELOPMENTAL TOXICITY (SEGMENT II) STUDY OF WR6026 DIHYDROCHLORIDE IN RABBITS

INDIVIDUAL FETAL MORPHOLOGICAL OBSERVATIONS

GROUP 3: 7 MG BASE/KG/DAY

Animal: 752 (CONT.)	Unique Fetal Id.: 6
Fetal Position: Left 06	
THORACIC CAVITY	
(Visceral)	HEART, MAJOR BLOOD VESSEL, VARIATION - VARIATION; LEFT
	SUBCLAVIAN ARISES FROM BRACHIOCEPHALIC TRUNK
RIBS	
(Skeletal)	RIB 13, FULL - VARIATION; BILATERAL
STERNUM	
(Skeletal)	STERNEBRA(E), MALALIGNED, SLIGHT TO MODERATE - VARIATION; 2, 3 AND 4, SLIGHT
	STERNEBRA(E), 5-6, UNOSSIFIED - VARIATION; 5 ONLY
Fetal Position: Left 07	Unique Fetal Id.: 7
NECK	
(Visceral)	THYROID, VARIATION - VARIATION; BILATERAL, REDDENED
RIBS	
(Skeletal)	RIB 13, FULL - VARIATION; BILATERAL
STERNUM	
(Skeletal)	STERNEBRA(E), 5-6, UNOSSIFIED - VARIATION; 5 ONLY
VERTEBRAL COLUMN	
(Skeletal)	VERTEBRAE, 27 PRESACRAL VERTEBRAE - VARIATION
SKULL	
(Skeletal)	HYOID BODY, UNOSSIFIED - VARIATION
Fetal Position: Right 01	Unique Fetal Id.: 8
NECK	
(Visceral)	THYROID, VARIATION - VARIATION; BILATERAL, REDDENED
THORACIC CAVITY	
(Visceral)	HEART, MAJOR BLOOD VESSEL, VARIATION - VARIATION; LEFT
	SUBCLAVIAN ARISES FROM BRACHIOCEPHALIC TRUNK
RIBS	
(Skeletal)	RIB 13, FULL - VARIATION; BILATERAL

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INDIVIDUAL FETAL MORPHOLOGICAL OBSERVATIONS

GROUP 3: 7 MG BASE/KG/DAY

Animal: 752 (CONT.)	Unique Fetal Id.: 9
Fetal Position: Right 02	
THORACIC CAVITY	
(Visceral) HEART, MAJOR BLOOD VESSEL, VARIATION - VARIATION; LEFT	
SUBCLAVIAN ARISES FROM BRACHIOCEPHALIC TRUNK	
Animal: 753	
Fetal Position: Left 01	Unique Fetal Id.: 1
RIBS	
(Skeletal) RIB 13, FULL - VARIATION; BILATERAL	
VERTEBRAL COLUMN	
(Skeletal) VERTEBRAE, 27 PRESACRAL VERTEBRAE - VARIATION	
Fetal Position: Left 02	Unique Fetal Id.: 2
RIBS	
(Skeletal) RIB 13, FULL - VARIATION; LEFT RUDIMENTARY, RIGHT FULL	
Fetal Position: Left 03	Unique Fetal Id.: 3
RIBS	
(Skeletal) RIB 13, FULL - VARIATION; BILATERAL	
Fetal Position: Right 01	Unique Fetal Id.: 5
RIBS	
(Skeletal) RIB 13, FULL - VARIATION; RIGHT	
Fetal Position: Right 02	Unique Fetal Id.: 6
RIBS	
(Skeletal) RIB 13, FULL - VARIATION; BILATERAL	
VERTEBRAL COLUMN	
(Skeletal) VERTEBRAE, 27 PRESACRAL VERTEBRAE - VARIATION	
Fetal Position: Right 03	Unique Fetal Id.: 7
RIBS	
(Skeletal) RIB 13, RUDIMENTARY - VARIATION; LEFT	

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INDIVIDUAL FETAL MORPHOLOGICAL OBSERVATIONS

GROUP 3: 7 MG BASE/KG/DAY

Animal: 754
Fetal Position: Left 02 Unique Fetal Id.: 2
RIBS
(Skeletal) RIB 13, RUDIMENTARY - VARIATION; RIGHT

Fetal Position: Left 06 Unique Fetal Id.: 6
RIBS
(Skeletal) RIB 13, FULL - VARIATION; BILATERAL

VERTEBRAL COLUMN

(Skeletal) VERTEBRAE, 27 PRESACRAL VERTEBRAE - VARIATION

Fetal Position: Right 01 Unique Fetal Id.: 7
RIBS
(Skeletal) RIB 13, RUDIMENTARY - VARIATION; LEFT (NO ARTICULATING HEAD)

Fetal Position: Right 02 Unique Fetal Id.: 8
RIBS
(Skeletal) RIB 13, FULL - VARIATION; BILATERAL

VERTEBRAL COLUMN

(Skeletal) VERTEBRAE, 27 PRESACRAL VERTEBRAE - VARIATION

Animal: 755
Fetal Position: Left 02 Unique Fetal Id.: 2
SKULL
(Skeletal) HYOID BODY, UNOSSIFIED - VARIATION

Fetal Position: Left 03 Unique Fetal Id.: 3
RIBS
(Skeletal) RIB 13, FULL - VARIATION; BILATERAL

VERTEBRAL COLUMN

(Skeletal) VERTEBRAE, 27 PRESACRAL VERTEBRAE - VARIATION

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INDIVIDUAL FETAL MORPHOLOGICAL OBSERVATIONS

GROUP 3: 7 MG BASE/KG/DAY

Animal: 755 (CONT.)

Fetal Position: Right 01 *
RIBS

Unique Fetal Id.: 4

(Skeletal) RIB 13, FULL - VARIATION; BILATERAL

VERTEBRAL COLUMN

(Skeletal) VERTEBRAE, 27 PRESACRAL VERTEBRAE - VARIATION

HINDLIMBS

(Skeletal) TALUS, UNOSSIFIED - VARIATION; BILATERAL

TAIL

(External) TAIL, ANOMALY - MALFORMATION; SHORT

Comments: SKELETAL CONFIRMATION OF SHORT TAIL: CAUDAL VERTEBRAE MALFORMED, FUSED OR ABSENT

Fetal Position: Right 02
RIBS

Unique Fetal Id.: 5

(Skeletal) RIB 13, FULL - VARIATION; BILATERAL

VERTEBRAL COLUMN

(Skeletal) VERTEBRAE, 27 PRESACRAL VERTEBRAE - VARIATION

Fetal Position: Right 04
RIBS

Unique Fetal Id.: 7

(Skeletal) RIB 13, FULL - VARIATION; BILATERAL

VERTEBRAL COLUMN

(Skeletal) VERTEBRAE, 27 PRESACRAL VERTEBRAE - VARIATION

Fetal Position: Right 05
RIBS

Unique Fetal Id.: 8

(Skeletal) RIB 13, RUDIMENTARY - VARIATION; LEFT (NO ARTICULATING HEAD)

VERTEBRAL COLUMN

(Skeletal) VERTEBRAE, 27 PRESACRAL VERTEBRAE - VARIATION

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INDIVIDUAL FETAL MORPHOLOGICAL OBSERVATIONS

GROUP 3: 7 MG BASE/KG/DAY

Animal: 757
Fetal Position: Left 01 Unique Fetal Id.: 1
RIBS
(Skeletal) RIB 13, FULL - VARIATION; LEFT FULL, RIGHT RUDIMENTARY

Fetal Position: Left 02 Unique Fetal Id.: 2
RIBS
(Skeletal) RIB 13, FULL - VARIATION; LEFT FULL, RIGHT RUDIMENTARY

ABDOMEN
(Visceral) URETER(S), RETROCAVAL - VARIATION; RIGHT

Fetal Position: Left 03 Unique Fetal Id.: 3
RIBS
(Skeletal) RIB 13, RUDIMENTARY - VARIATION; RIGHT

Fetal Position: Right 01 Unique Fetal Id.: 7
RIBS
(Skeletal) RIB 13, RUDIMENTARY - VARIATION; LEFT

Fetal Position: Right 02 Unique Fetal Id.: 8
RIBS
(Skeletal) RIB 13, RUDIMENTARY - VARIATION; RIGHT

STERNUM
(Skeletal) STERNEBRA(E), MALALIGNED, SLIGHT TO MODERATE - VARIATION; 5, SLIGHT

Animal: 758
Fetal Position: Left 02 Unique Fetal Id.: 2
RIBS
(Skeletal) RIB 13, RUDIMENTARY - VARIATION; LEFT

Fetal Position: Left 04 Unique Fetal Id.: 4
RIBS
(Skeletal) RIB 13, RUDIMENTARY - VARIATION; BILATERAL (NO ARTICULATING HEADS)

SKULL
(Skeletal) HYOID ARCH(ES), BENT - VARIATION; RIGHT, MODERATE

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INDIVIDUAL FETAL MORPHOLOGICAL OBSERVATIONS

GROUP 3: 7 MG BASE/KG/DAY

Animal: 758 (CONT.)		Unique Fetal Id.: 5
Fetal Position: Left 05	THORACIC CAVITY	
(Visceral)	HEART, MAJOR BLOOD VESSEL, VARIATION - VARIATION; LEFT CAROTID ARISES FROM THE BRACHIOCEPHALIC TRUNK	
RIBS		
(Skeletal)	RIB 13, FULL - VARIATION; LEFT FULL, RIGHT RUDIMENTARY	
Fetal Position: Right 02		Unique Fetal Id.: 9
RIBS		
(Skeletal)	RIB 13, RUDIMENTARY - VARIATION; BILATERAL	
Animal: 759		
Fetal Position: Left 01		Unique Fetal Id.: 1
RIBS		
(Skeletal)	RIB 13, FULL - VARIATION; BILATERAL	
Fetal Position: Left 02		Unique Fetal Id.: 2
RIBS		
(Skeletal)	RIB 13, FULL - VARIATION; BILATERAL	
EYES		
(Visceral)	AROUND IRIS, HEMORRHAGIC RING - VARIATION	
Fetal Position: Left 03		Unique Fetal Id.: 3
RIBS		
(Skeletal)	RIB 13, RUDIMENTARY - VARIATION; RIGHT (NO ARTICULATING HEAD)	
Fetal Position: Left 04		Unique Fetal Id.: 4
SKULL		
(Skeletal)	HYOID BODY, UNOSSIFIED - VARIATION	
Fetal Position: Left 05		Unique Fetal Id.: 5
RIBS		
(Skeletal)	RIB 13, FULL - VARIATION; LEFT FULL, RIGHT RUDIMENTARY	

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INDIVIDUAL FETAL MORPHOLOGICAL OBSERVATIONS

GROUP 3: 7 MG BASE/KG/DAY

Animal: 759 (CONT.)	Unique Fetal Id.: 6
Fetal Position: Right 01	
RIBS	
(Skeletal) RIB 13, RUDIMENTARY - VARIATION; LEFT	
Animal: 760	
Fetal Position: Left 01	Unique Fetal Id.: 1
THORACIC CAVITY	
(Visceral) HEART, MAJOR BLOOD VESSEL, VARIATION - VARIATION;	
ACCESSORY LEFT SUBCLAVIAN, LEFT CAROTID ARISES FROM THE	
BRACHIOCEPHALIC TRUNK	
Fetal Position: Left 02	Unique Fetal Id.: 2
RIBS	
(Skeletal) RIB 13, FULL - VARIATION; BILATERAL	
VERTEBRAL COLUMN	
(Skeletal) VERTEBRAE, 27 PRESACRAL VERTEBRAE - VARIATION	
Fetal Position: Right 01	Unique Fetal Id.: 3
RIBS	
(Skeletal) RIB 13, FULL - VARIATION; LEFT FULL, RIGHT RUDIMENTARY	
SKULL	
(Skeletal) HYOID ARCH(ES), BENT - VARIATION; RIGHT, MODERATE	
Fetal Position: Right 02	Unique Fetal Id.: 4
THORACIC CAVITY	
(Visceral) HEART, MAJOR BLOOD VESSEL, VARIATION - VARIATION; LEFT	
CAROTID ARISES FROM THE BRACHIOCEPHALIC TRUNK	
RIBS	
(Skeletal) RIB 13, FULL - VARIATION; LEFT FULL, RIGHT RUDIMENTARY	

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INDIVIDUAL FETAL MORPHOLOGICAL OBSERVATIONS

GROUP 4: 15/10 MG BASE/KG/DAY

Animal: 761		
Fetal Position: Left 01		Unique Fetal Id.: 1
RIBS		
(Skeletal) RIB 13, FULL - VARIATION; LEFT FULL, RIGHT RUDIMENTARY		
Fetal Position: Left 02		Unique Fetal Id.: 2
STERNUM		
(Skeletal) STERNEBRA(E), 5-6, UNOSSIFIED - VARIATION; 5 ONLY		
Fetal Position: Left 03		Unique Fetal Id.: 3
RIBS		
(Skeletal) RIB 13, FULL - VARIATION; BILATERAL		
VERTEBRAL COLUMN		
(Skeletal) VERTEBRAE, 27 PRESACRAL VERTEBRAE - VARIATION		
Fetal Position: Left 04		Unique Fetal Id.: 4
RIBS		
(Skeletal) RIB 13, FULL - VARIATION; BILATERAL		
VERTEBRAL COLUMN		
(Skeletal) VERTEBRAE, 27 PRESACRAL VERTEBRAE - VARIATION		
SKULL		
(Skeletal) HYOID ARCH(ES), BENT - VARIATION; RIGHT, SLIGHT		
Fetal Position: Right 01		Unique Fetal Id.: 6
RIBS		
(Skeletal) RIB 13, FULL - VARIATION; BILATERAL		
Fetal Position: Right 03		Unique Fetal Id.: 8
RIBS		
(Skeletal) RIB 13, FULL - VARIATION; LEFT FULL, RIGHT RUDIMENTARY		

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INDIVIDUAL FETAL MORPHOLOGICAL OBSERVATIONS

GROUP 4: 15/10 MG BASE/KG/DAY

Animal: 761 (CONT.)
Fetal Position: Right 05 Unique Fetal Id.: 10
RIBS
(Skeletal) RIB 13, FULL - VARIATION; RIGHT

Fetal Position: Right 06 Unique Fetal Id.: 11
RIBS
(Skeletal) RIB 13, RUDIMENTARY - VARIATION; BILATERAL

STERNUM
(Skeletal) STERNEBRA(E), MALALIGNED, SLIGHT TO MODERATE - VARIATION;
2, 3 AND 4, SLIGHT

SKULL
(Skeletal) HYOID BODY, UNOSSIFIED - VARIATION

HINDLIMBS
(Skeletal) TALUS, UNOSSIFIED - VARIATION; BILATERAL

Fetal Position: Right 07 Unique Fetal Id.: 12
RIBS
(Skeletal) RIB 13, FULL - VARIATION; BILATERAL

VERTEBRAL COLUMN
(Skeletal) VERTEBRAE, 27 PRESACRAL VERTEBRAE - VARIATION

Animal: 762
Fetal Position: Left 01 Unique Fetal Id.: 1
STERNUM
(Skeletal) STERNEBRA(E), 5-6, UNOSSIFIED - VARIATION; 5 ONLY

Note: For Dam 761, Fetuses 11 and 12, a visceral examination of the brain by midsagittal slice was not performed.

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INDIVIDUAL FETAL MORPHOLOGICAL OBSERVATIONS

GROUP 4: 15/10 MG BASE/KG/DAY

Animal: 762 (CONT.)
Fetal Position: Left 02 Unique Fetal Id.: 2
RIBS (Skeletal) RIB 13, FULL - VARIATION; BILATERAL

STERNUM
(Skeletal) STERNEBRA (E), MALALIGNED, SLIGHT TO MODERATE - VARIATION;
2, 3 AND 4, SLIGHT
STERNEBRA (E), 5-6, UNOSSIFIED - VARIATION; 5 ONLY

Fetal Position: Left 03 Unique Fetal Id.: 3
THORACIC CAVITY (Visceral) HEART, MAJOR BLOOD VESSEL, VARIATION - VARIATION; LEFT
CAROTID ARISES FROM BRACHIOCEPHALIC TRUNK

RIBS (Skeletal) RIB 13, FULL - VARIATION; BILATERAL

Fetal Position: Left 04 Unique Fetal Id.: 4
THORACIC CAVITY (Visceral) HEART, MAJOR BLOOD VESSEL, VARIATION - VARIATION; LEFT
CAROTID ARISES FROM BRACHIOCEPHALIC TRUNK

Fetal Position: Right 01 Unique Fetal Id.: 6
RIBS (Skeletal) RIB 13, RUDIMENTARY - VARIATION; RIGHT (NO ARTICULATING
HEAD)

STERNUM
(Skeletal) STERNEBRA (E), 5-6, UNOSSIFIED - VARIATION; 5 ONLY

Fetal Position: Right 03 Unique Fetal Id.: 8
THORACIC CAVITY (Visceral) HEART, MAJOR BLOOD VESSEL, VARIATION - VARIATION; LEFT
CAROTID ARISES FROM THE BRACHIOCEPHALIC TRUNK

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UIC/TRL STUDY NO. 173 DEVELOPMENTAL TOXICITY (SEGMENT II) STUDY OF WR6026 DIHYDROCHLORIDE IN RABBITS

INDIVIDUAL FETAL MORPHOLOGICAL OBSERVATIONS

GROUP 4: 15/10 MG BASE/KG/DAY

Animal: 762 (CONT.)	Unique Fetal Id.: 9
Fetal Position: Right 04	
STERNUM	
(Skeletal) STERNEBRA(E), 5-6, UNOSSIFIED - VARIATION; 5 ONLY	
Fetal Position: Right 05	Unique Fetal Id.: 10
STERNUM	
(Skeletal) STERNEBRA(E), 5-6, UNOSSIFIED - VARIATION; 5 ONLY	
ABDOMEN	
(Visceral) URETER(S), RETROCAVAL - VARIATION; RIGHT SIDE	
Fetal Position: Right 06	Unique Fetal Id.: 11
RIBS	
(Skeletal) RIB 13, FULL - VARIATION; LEFT RUDIMENTARY, RIGHT FULL	
SKULL	
(Skeletal) HYOID ARCH(ES), BENT - VARIATION; RIGHT, SLIGHT	
Animal: 766	Unique Fetal Id.: 1
Fetal Position: Left 01	
RIBS	
(Skeletal) RIB 13, FULL - VARIATION; BILATERAL	
STERNUM	
(Skeletal) STERNEBRA(E), 5-6, UNOSSIFIED - VARIATION; 6 ONLY	
VERTEBRAL COLUMN	
(Skeletal) VERTEBRAE, 27 PRESACRAL VERTEBRAE - VARIATION	
VERTEBRAE, ANOMALY - MALFORMATION; INVOLVING CERVICAL	
VERTEBRA 7 AND THORACIC VERTEBRA 1	

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INDIVIDUAL FETAL MORPHOLOGICAL OBSERVATIONS

GROUP 4: 15/10 MG BASE/KG/DAY

Animal: 766 (CONT.)
 Fetal Position: Left 02 * Unique Fetal Id.: 2
 STERNUM
 (Skeletal) STERNEBRA(E), MALALIGNED, SEVERE - MALFORMATION; 3
 MODERATE, 4 SEVERE
 STERNEBRA(E), 5-6, UNOSSIFIED - VARIATION

VERTEBRAL COLUMN
 (Skeletal) VERTEBRAE/RIBS, ANOMALY - MALFORMATION; ADDITIONAL
 CERVICAL VERTEBRAE LOCATED BETWEEN EXOCCIPITALS AND
 CERVICAL VERTEBRA 1, THE CENTRA OF THE ADDITIONAL
 VERTEBRAE AND CERVICAL VERTEBRA NUMBER 1 ARE MALFORMED AND
 FUSED, THORACIC VERTEBRAE 7 THROUGH 11 MALFORMED, RIGHT
 RIBS 8 AND 9 PROXIMAL ENDS MALFORMED, LUMBAR VERTEBRA
 NUMBER 3 MALFORMED, REMAINING LUMBAR VERTEBRAE AND ALL
 SACRAL VERTEBRAE ABSENT

TAIL
 (External) TAIL, ANOMALY - MALFORMATION; THREADLIKE

ABDOMEN
 (Visceral) GALL BLADDER, VARIATION - VARIATION; SMALL
 KIDNEY(S) AND/OR URETER(S), ANOMALY - MALFORMATION; LEFT
 URETER ABSENT, LEFT KIDNEY ABSENT, RIGHT KIDNEY SMALL,
 MALFORMED AND UNASCENDED

Comments: SKELETAL CONFIRMATION OF THREADLIKE TAIL: ALL CAUDAL VERTEBRAE ABSENT

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INDIVIDUAL FETAL MORPHOLOGICAL OBSERVATIONS

GROUP 4: 15/10 MG BASE/KG/DAY

Animal: 766 (CONT.)
Fetal Position: Left 03 Unique Fetal Id.: 3
RIBS
(Skeletal) RIB 13, FULL - VARIATION; LEFT

STERNUM
(Skeletal) STERNEBRA(E), MALALIGNED, SLIGHT TO MODERATE - VARIATION;
3 AND 4, SLIGHT
STERNEBRA(E), 5-6, UNOSSIFIED - VARIATION; 5 ONLY

VERTEBRAL COLUMN
(Skeletal) VERTEBRAE, 8 CERVICAL VERTEBRAE - MALFORMATION

ABDOMEN
(Visceral) GALL BLADDER, VARIATION - VARIATION; ABSENT

Fetal Position: Left 04 Unique Fetal Id.: 4
THORACIC CAVITY
(Visceral) DIAPHRAGM, DIAPHRAGMATIC HERNIA - MALFORMATION; ANTERIOR
PORTION OF STOMACH PROTRUDES INTO THORACIC CAVITY

VERTEBRAL COLUMN
(Skeletal) VERTEBRAE/RIBS, ANOMALY - MALFORMATION; INVOLVING ALL
VERTEBRAE EITHER ADDITIONAL, MALFORMED, ABSENT OR FUSED,
STERNEBRAE MALFORMED DUE TO MALFORMATION OF RIBS

ABDOMEN
(Visceral) GALL BLADDER, VARIATION - VARIATION; SMALL
KIDNEY(S) AND/OR URETER(S), ANOMALY - MALFORMATION; RIGHT
KIDNEY ABSENT AND RIGHT URETER ABSENT

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UIC/TRL STUDY NO. 173 DEVELOPMENTAL TOXICITY (SEGMENT II) STUDY OF WR6026 DIHYDROCHLORIDE IN RABBITS

INDIVIDUAL FETAL MORPHOLOGICAL OBSERVATIONS

GROUP 4: 15/10 MG BASE/KG/DAY

Animal: 766 (CONT.)	Unique Fetal Id.: 5
Fetal Position: Right 01	
THORACIC CAVITY	
(Visceral)	HEART, HEART AND/OR GREAT VESSEL, ANOMALY - MALFORMATION; RETROESOPHAGEAL AORTIC ARCH (LEFT CAROTID ARISES FROM BRACHIOCEPHALIC TRUNK), INTERVENTRICULAR SEPTAL DEFECT
STERNUM	
(Skeletal)	STERNEBRA(E), 5-6, UNOSSIFIED - VARIATION; 5 ONLY
VERTEBRAL COLUMN	
(Skeletal)	VERTEBRAE/RIBS, ANOMALY - MALFORMATION; INVOLVING ALL CERVICAL VERTEBRAE, THORACIC VERTEBRAE 1 THROUGH 7, RIGHT RIBS 3 AND 4, LEFT RIBS 10, 11, 3 AND 4 EITHER ADDITIONAL, MALFORMED, ABSENT OR FUSED; STERNEBRAE MALALIGNED: 2 AND 3 MODERATE, 1 SLIGHT, 4 SEVERE
EYES	
(Visceral)	EYE(S), ANOPHTHALMIA/MICROPHTHALMIA - MALFORMATION; BILATERAL MICROPHTHALMIA
ABDOMEN	
(Visceral)	KIDNEY(S) AND/OR URETER(S), ANOMALY - MALFORMATION; BILATERAL KIDNEYS AND URETERS ABSENT
HEAD	
(Visceral)	BRAIN, HYDROCEPHALY - MALFORMATION; BILATERAL, INTERNAL

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UIC/TRL STUDY NO. 173 DEVELOPMENTAL TOXICITY (SEGMENT II) STUDY OF WR6026 DIHYDROCHLORIDE IN RABBITS

INDIVIDUAL FETAL MORPHOLOGICAL OBSERVATIONS

GROUP 4: 15/10 MG BASE/KG/DAY

Animal: 766 (CONT.)

Fetal Position: Right 03

THORACIC CAVITY

(Visceral)

HEART, MAJOR BLOOD VESSEL, VARIATION - VARIATION; LEFT CAROTID ARISES FROM THE BRACHIOCEPHALIC TRUNK, ACCESSORY LEFT SUBCLAVIAN

Unique Fetal Id.: 7

RIBS

(Skeletal) RIB 13, FULL - VARIATION; BILATERAL

STERNUM

(Skeletal) STERNEBRA(E), MALALIGNED, SLIGHT TO MODERATE - VARIATION; 4, SLIGHT

STERNEBRA(E), 5-6, UNOSSIFIED - VARIATION; 5 ONLY

VERTEBRAL COLUMN

(Skeletal) VERTEBRAE, 8 CERVICAL VERTEBRAE - MALFORMATION; 28

PRESACRAL VERTEBRAE

VERTEBRAE, ANOMALY - MALFORMATION; CERVICAL CENTRA 5-8 MALFORMED, 1 MALFORMED

ABDOMEN

(Visceral) GALL BLADDER, VARIATION - VARIATION; SMALL

Fetal Position: Right 04

RIBS

Unique Fetal Id.: 8

(Skeletal) RIB 13, FULL - VARIATION; BILATERAL

VERTEBRAL COLUMN

(Skeletal) VERTEBRAE, 27 PRESACRAL VERTEBRAE - VARIATION

SKULL

(Skeletal) HYOID ARCH(ES), BENT - VARIATION; BILATERAL, SLIGHT

ABDOMEN

(Visceral) GALL BLADDER, VARIATION - VARIATION; SMALL

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UIC/TRL STUDY NO. 173 DEVELOPMENTAL TOXICITY (SEGMENT II) STUDY OF WR6026 DIHYDROCHLORIDE IN RABBITS

INDIVIDUAL FETAL MORPHOLOGICAL OBSERVATIONS

GROUP 4: 15/10 MG BASE/KG/DAY

Animal: 767		
Fetal Position: Left 01	Unique Fetal Id.: 1	
STERNUM		
(Skeletal) STERNEBRA(E), MALALIGNED, SLIGHT TO MODERATE - VARIATION; 5 AND 6, SLIGHT		
Fetal Position: Left 02	Unique Fetal Id.: 2	
RIBS		
(Skeletal) RIB 13, RUDIMENTARY - VARIATION; LEFT		
STERNUM		
(Skeletal) STERNEBRA(E), VARIATION - VARIATION; 6 FORKED, DISTAL PORTION; COSTAL CARTILAGE ARTICULATES WITH END OF THE FORK		
Fetal Position: Left 03	Unique Fetal Id.: 3	
THORACIC CAVITY		
(Visceral) HEART, MAJOR BLOOD VESSEL, VARIATION - VARIATION; LEFT CAROTID ARISES FROM BRACHIOCEPHALIC TRUNK		
RIBS		
(Skeletal) RIB 13, RUDIMENTARY - VARIATION; LEFT (NO ARTICULATING HEAD)		
STERNUM		
(Skeletal) STERNEBRA(E), VARIATION - VARIATION; 6 FORKED, DISTAL PORTION; COSTAL CARTILAGE ARTICULATES WITH END OF FORK		
STERNEBRA(E), MALALIGNED, SLIGHT TO MODERATE - VARIATION; 5, SLIGHT		
Fetal Position: Right 02	Unique Fetal Id.: 5	
THORACIC CAVITY		
(Visceral) HEART, MAJOR BLOOD VESSEL, VARIATION - VARIATION; LEFT CAROTID ARISES FROM BRACHIOCEPHALIC TRUNK		
Fetal Position: Right 03	Unique Fetal Id.: 6	
RIBS		
(Skeletal) RIB 13, FULL - VARIATION; LEFT FULL, RIGHT RUDIMENTARY		

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INDIVIDUAL FETAL MORPHOLOGICAL OBSERVATIONS

GROUP 4: 15/10 MG BASE/KG/DAY

Animal: 767 (CONT.)		
Fetal Position:	Right 04	Unique Fetal Id.: 7
RIBS	(Skeletal) RIB 13, FULL - VARIATION; BILATERAL	
Animal: 768		
Fetal Position:	Left 01	Unique Fetal Id.: 1
RIBS	(Skeletal) RIB 13, FULL - VARIATION; RIGHT (SMALL ARTICULATING HEAD)	
Fetal Position:	Left 02	Unique Fetal Id.: 2
RIBS	(Skeletal) RIB 13, FULL - VARIATION; BILATERAL	
VERTEBRAL COLUMN		
	(Skeletal) VERTEBRAE, 27 PRESACRAL VERTEBRAE - VARIATION	
Fetal Position:	Left 03	Unique Fetal Id.: 3
STERNUM	(Skeletal) STERNEBRA(E), MALALIGNED AND FUSED - MALFORMATION; 4 AND 5 FUSED; 2-5, MALALIGNED SLIGHT	
Fetal Position:	Right 01	Unique Fetal Id.: 4
STERNUM	(Skeletal) STERNEBRA(E), MALALIGNED, SLIGHT TO MODERATE - VARIATION; 5, SLIGHT	
Fetal Position:	Right 02	Unique Fetal Id.: 5
THORACIC CAVITY	(Visceral) HEART, MAJOR BLOOD VESSEL, VARIATION - VARIATION; ACCESSORY LEFT SUBCLAVIAN	
ABDOMEN		
	(Visceral) GALL BLADDER, VARIATION - VARIATION; SMALL	

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INDIVIDUAL FETAL MORPHOLOGICAL OBSERVATIONS

GROUP 4: 15/10 MG BASE/KG/DAY

Animal: 768(CONT.)
 Fetal Position: Right 03
 STERNUM
 (Skeletal) STERNEBRA(E), MALALIGNED, SLIGHT TO MODERATE - VARIATION; 5, SLIGHT

Unique Fetal Id.: 6

Fetal Position: Right 04
 RIBS
 (Skeletal) RIB 13, FULL - VARIATION; BILATERAL

Unique Fetal Id.: 7

ABDOMEN
 (Visceral) URETER(S), RETROCAVAL - VARIATION; RIGHT SIDE

Animal: 769

Comments: ID LABELS FOR FETUSES 4 AND 5 FOUND SEPARATED FROM TAGS AT START OF SKELETAL EXAM. THESE TWO FETUSES WERE RANDOMLY REASSIGNED ID NUMBERS BEFORE BEING EXAMINED SKELETALLY.

Fetal Position: Right 01 *
 RIBS
 (Skeletal) RIB 13, FULL - VARIATION; LEFT

Unique Fetal Id.: 4

VERTEBRAL COLUMN
 (Skeletal) VERTEBRAE, 27 PRESACRAL VERTEBRAE - VARIATION

Fetal Position: Right 04
 RIBS
 (Skeletal) RIB 13, FULL - VARIATION; BILATERAL

Unique Fetal Id.: 7

STERNUM
 (Skeletal) STERNEBRA(E), FUSED - MALFORMATION; 3, 4 AND 5

VERTEBRAL COLUMN
 (Skeletal) VERTEBRAE, 27 PRESACRAL VERTEBRAE - VARIATION

SKULL
 (Skeletal) HYOID ARCH(ES), BENT - VARIATION; RIGHT, SLIGHT

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INDIVIDUAL FETAL MORPHOLOGICAL OBSERVATIONS

GROUP 4: 15/10 MG BASE/KG/DAY

Animal: 770			
Fetal Position: Left 01		Unique Fetal Id.: 1	
STERNUM			
(Skeletal) STERNEBRA(E), 5-6, UNOSSIFIED - VARIATION; 5 ONLY			
Fetal Position: Left 02		Unique Fetal Id.: 2	
STERNUM			
(Skeletal) STERNEBRA(E), MALALIGNED, SLIGHT TO MODERATE - VARIATION; 5, SLIGHT			
Fetal Position: Left 03		Unique Fetal Id.: 3	
RIBS			
(Skeletal) RIB 13, FULL - VARIATION; BILATERAL			
Fetal Position: Right 01		Unique Fetal Id.: 5	
RIBS			
(Skeletal) RIB 13, RUDIMENTARY - VARIATION; BILATERAL			
Fetal Position: Right 02		Unique Fetal Id.: 6	
RIBS			
(Skeletal) RIB 13, FULL - VARIATION; LEFT			
Fetal Position: Right 04		Unique Fetal Id.: 8	
RIBS			
(Skeletal) RIB 13, RUDIMENTARY - VARIATION; LEFT			
STERNUM			
(Skeletal) STERNEBRA(E), 5-6, UNOSSIFIED - VARIATION; 6 ONLY			
Animal: 771			
Fetal Position: Left 03		Unique Fetal Id.: 3	
RIBS			
(Skeletal) RIB 13, RUDIMENTARY - VARIATION; LEFT (NO ARTICULATING HEAD)			

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INDIVIDUAL FETAL MORPHOLOGICAL OBSERVATIONS

GROUP 4: 15/10 MG BASE/KG/DAY

Animal: 771 (CONT.)	Unique Fetal Id.: 4
Fetal Position: Left 04	
THORACIC CAVITY	
(Visceral) HEART, MAJOR BLOOD VESSEL, VARIATION - VARIATION; ACCESSORY LEFT SUBCLAVIAN	
RIBS	
(Skeletal) 7TH CERVICAL RIB, PRESENT - VARIATION; RIGHT	
Fetal Position: Right 02	Unique Fetal Id.: 6
STERNUM	
(Skeletal) STERNEBRA(E), 5-6, UNOSSIFIED - VARIATION; 5 ONLY	
Fetal Position: Right 03	Unique Fetal Id.: 7
STERNUM	
(Skeletal) STERNEBRA(E), MALALIGNED, SLIGHT TO MODERATE - VARIATION; 5, SLIGHT	
Animal: 772	
Fetal Position: Left 01	Unique Fetal Id.: 1
THORACIC CAVITY	
(Visceral) HEART, MAJOR BLOOD VESSEL, VARIATION - VARIATION; LEFT	
CAROTID ARISES FROM THE BRACHIOCEPHALIC TRUNK	
Fetal Position: Left 02	Unique Fetal Id.: 2
THORACIC CAVITY	
(Visceral) HEART, MAJOR BLOOD VESSEL, VARIATION - VARIATION; LEFT	
CAROTID ARISES FROM BRACHIOCEPHALIC TRUNK	
VERTEBRAL COLUMN	
(Skeletal) VERTEBRAE, 27 PRESACRAL VERTEBRAE - VARIATION	
Fetal Position: Right 01	Unique Fetal Id.: 5
RIBS	
(Skeletal) RIB 13, FULL - VARIATION; LEFT	
SKULL	
(Skeletal) HYOID ARCH(ES), BENT - VARIATION; LEFT, SLIGHT	

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INDIVIDUAL FETAL MORPHOLOGICAL OBSERVATIONS

GROUP 4: 15/10 MG BASE/KG/DAY

Animal: 772 (CONT.)	Unique Fetal Id.: 8
Fetal Position: Right 04	
THORACIC CAVITY	
(Visceral) HEART, MAJOR BLOOD VESSEL, VARIATION - VARIATION; LEFT	
CAROTID ARISES FROM THE BRACHIOCEPHALIC TRUNK	
Animal: 773	Unique Fetal Id.: 1
Fetal Position: Left 01	
RIBS	
(Skeletal) RIB 13, FULL - VARIATION; LEFT RUDIMENTARY, RIGHT FULL	
Fetal Position: Left 02	Unique Fetal Id.: 2
THORACIC CAVITY	
(Visceral) HEART, MAJOR BLOOD VESSEL, VARIATION - VARIATION; LEFT	
CAROTID ARISES FROM THE BRACHIOCEPHALIC TRUNK, ACCESSORY	
LEFT SUBCLAVIAN	
RIBS	
(Skeletal) RIB 13, FULL - VARIATION; BILATERAL	
VERTEBRAL COLUMN	
(Skeletal) VERTEBRAE, 27 PRESACRAL VERTEBRAE - VARIATION	
Fetal Position: Right 02	Unique Fetal Id.: 4
RIBS	
(Skeletal) RIB 13, FULL - VARIATION; BILATERAL	
Fetal Position: Right 03	Unique Fetal Id.: 5
RIBS	
(Skeletal) RIB 13, FULL - VARIATION; BILATERAL	
VERTEBRAL COLUMN	
(Skeletal) VERTEBRAE, 27 PRESACRAL VERTEBRAE - VARIATION	
SKULL	
(Skeletal) HYOID ARCH(ES), BENT - VARIATION; BILATERAL, SLIGHT	

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INDIVIDUAL FETAL MORPHOLOGICAL OBSERVATIONS

GROUP 4: 15/10 MG BASE/KG/DAY

Animal: 773 (CONT.) Unique Fetal Id.: 6
Fetal Position: Right 04
RIBS (Skeletal) RIB 13, RUDIMENTARY - VARIATION; LEFT

STERNUM
(Skeletal) STERNEBRA(E), MALALIGNED, SLIGHT TO MODERATE - VARIATION;
2, 3 AND 4, SLIGHT
STERNEBRA(E), 5-6, UNOSSIFIED - VARIATION; 5 ONLY

SKULL
(Skeletal) HYOID ARCH(ES), BENT - VARIATION; LEFT, MODERATE

Animal: 774 Unique Fetal Id.: 1
Fetal Position: Left 01
RIBS (Skeletal) RIB 13, FULL - VARIATION; BILATERAL

Fetal Position: Left 02 Unique Fetal Id.: 2
RIBS (Skeletal) RIB 13, FULL - VARIATION; BILATERAL

Fetal Position: Left 03 Unique Fetal Id.: 3
STERNUM (Skeletal) STERNEBRA(E), MALALIGNED, SLIGHT TO MODERATE - VARIATION;
3 AND 4, SLIGHT

Fetal Position: Right 01 Unique Fetal Id.: 5
RIBS (Skeletal) RIB 13, FULL - VARIATION; BILATERAL

VERTEBRAL COLUMN
(Skeletal) VERTEBRAE, 27 PRESACRAL VERTEBRAE - VARIATION

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INDIVIDUAL FETAL MORPHOLOGICAL OBSERVATIONS

GROUP 4: 15/10 MG BASE/KG/DAY

Animal: 774 (CONT.)		Unique Fetal Id.: 6
Fetal Position:	Right 02	
RIBS		
(Skeletal) RIB 13,	FULL - VARIATION; BILATERAL	
VERTEBRAL COLUMN		
(Skeletal) VERTEBRAE,	27 PRESACRAL VERTEBRAE - VARIATION	
Fetal Position:	Right 03	Unique Fetal Id.: 7
RIBS		
(Skeletal) RIB 13,	FULL - VARIATION; BILATERAL	
Fetal Position:	Right 04	Unique Fetal Id.: 8
RIBS		
(Skeletal) RIB 13,	FULL - VARIATION; LEFT FULL, RIGHT RUDIMENTARY	
Fetal Position:	Right 05	Unique Fetal Id.: 9
RIBS		
(Skeletal) RIB 13,	FULL - VARIATION; BILATERAL	
Fetal Position:	Right 06	Unique Fetal Id.: 10
RIBS		
(Skeletal) RIB 13,	FULL - VARIATION; BILATERAL	

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INDIVIDUAL FETAL MORPHOLOGICAL OBSERVATIONS

GROUP 4: 15/10 MG BASE/KG/DAY

Animal: 776

Fetal Position: Left 01

Unique Fetal Id.: 1

THORACIC CAVITY

(Visceral) HEART, MAJOR BLOOD VESSEL, VARIATION - VARIATION; LEFT CAROTID ARISES FROM THE BRACHIOCEPHALIC TRUNK

RIBS

(Skeletal) RIB 13, FULL - VARIATION; BILATERAL

STERNUM

(Skeletal) STERNEBRA (E), MALALIGNED, SLIGHT TO MODERATE - VARIATION; 5, SLIGHT

ABDOMEN

(Visceral) KIDNEY(S), HYDRONEPHROSIS - VARIATION; RIGHT, SLIGHT URETER(S), RETROCAVAL - VARIATION; RIGHT

Fetal Position: Left 02

Unique Fetal Id.: 2

VERTEBRAL COLUMN

(Skeletal) VERTEBRAE/RIBS, ANOMALY - MALFORMATION; CERVICAL CENTRA 1 THROUGH 3 MALFORMED, VENTRAL ASPECT OF LEFT CERVICAL ARCH NUMBER 7 AND LEFT THORACIC ARCH NUMBER 1 MALFORMED, LEFT RIB NUMBER 1 ABSENT; 13TH FULL RIB, BILATERAL; 27 PRESACRAL VERTEBRAE

ABDOMEN

(Visceral) KIDNEY(S), HYDRONEPHROSIS - VARIATION; BILATERAL, SLIGHT

Fetal Position: Left 03

Unique Fetal Id.: 3

THORACIC CAVITY

(Visceral) HEART, MAJOR BLOOD VESSEL, VARIATION - VARIATION; LEFT CAROTID ARISES FROM THE BRACHIOCEPHALIC TRUNK

RIBS

(Skeletal) RIB 13, FULL - VARIATION; BILATERAL

VERTEBRAL COLUMN

(Skeletal) VERTEBRAE, 27 PRESACRAL VERTEBRAE - VARIATION

ABDOMEN

(Visceral) KIDNEY(S), HYDRONEPHROSIS - VARIATION; BILATERAL, SLIGHT

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INDIVIDUAL FETAL MORPHOLOGICAL OBSERVATIONS

GROUP 4: 15/10 MG BASE/KG/DAY

Animal: 776 (CONT.)	Unique Fetal Id.: 4
Fetal Position: Left 04	
THORACIC CAVITY	
(Visceral) HEART, MAJOR BLOOD VESSEL, VARIATION - VARIATION; LEFT	
CAROTID ARISES FROM THE BRACHIOCEPHALIC TRUNK	
RIBS	
(Skeletal) RIB 13, FULL - VARIATION; LEFT	
ABDOMEN	
(Visceral) KIDNEY(S), HYDRONEPHROSIS - VARIATION; BILATERAL, SLIGHT	
Fetal Position: Right 01	Unique Fetal Id.: 5
THORACIC CAVITY	
(Visceral) HEART, MAJOR BLOOD VESSEL, VARIATION - VARIATION; LEFT	
CAROTID ARISES FROM THE BRACHIOCEPHALIC TRUNK, ACCESSORY	
LEFT SUBCLAVIAN	
RIBS	
(Skeletal) RIB 13, FULL - VARIATION; BILATERAL (RIGHT--NO	
ARTICULATING HEAD)	
STERNUM	
(Skeletal) STERNEBRA(E), MALALIGNED, SLIGHT TO MODERATE - VARIATION;	
5, SLIGHT	
VERTEBRAL COLUMN	
(Skeletal) VERTEBRAE, 27 PRESACRAL VERTEBRAE - VARIATION	

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INDIVIDUAL FETAL MORPHOLOGICAL OBSERVATIONS

GROUP 4: 15/10 MG BASE/KG/DAY

Animal: 776 (CONT.)

Fetal Position: Right 02

Unique Fetal Id.: 6

THORACIC CAVITY

(Visceral) HEART, MAJOR BLOOD VESSEL, VARIATION - VARIATION; LEFT CAROTID ARISES FROM THE BRACHIOCEPHALIC TRUNK

STERNUM

(Skeletal) STERNEBRA(E), MALALIGNED, SLIGHT TO MODERATE - VARIATION; 2-5, SLIGHT

VERTEBRAL COLUMN

(Skeletal) VERTEBRAE/RIBS, ANOMALY - MALFORMATION; CERVICAL CENTRA 1 AND 2, THORACIC 7 THROUGH 13 CENTRA AND ARCHES, RIGHT RIBS 8 THROUGH 11 MALFORMED, FUSED OR ABSENT; 13TH FULL RIB, BILATERAL, 27 PRESACRAL VERTEBRAE

ABDOMEN

(Visceral) SPLEEN, SMALL IN SIZE - VARIATION

Fetal Position: Right 03

Fetal Type: Non-Viable Fetus

Comments: Crown-Rump Length: 75 mm

Fetal Position: Right 04

STERNUM

(Skeletal) STERNEBRA(E), 1-4, UNOSSIFIED - VARIATION; 1 ONLY
STERNEBRA(E), 5-6, UNOSSIFIED - VARIATION; 5 ONLY

Unique Fetal Id.: 8

VERTEBRAL COLUMN

(Skeletal) VERTEBRAE, 8 CERVICAL VERTEBRAE - MALFORMATION; BILATERAL 8TH CERVICAL RIB PRESENT
VERTEBRAE/RIBS, ANOMALY - MALFORMATION; THORACIC VERTEBRAE 9 AND 10 MALFORMED AND FUSED, LEFT RIBS 9 AND 10 CLOSER TOGETHER THAN NORMAL AT PROXIMAL END; 27 PRESACRAL VERTEBRAE

ABDOMEN

(Visceral) KIDNEY(S), HYDRONEPHROSIS - VARIATION; BILATERAL, SLIGHT

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INDIVIDUAL FETAL MORPHOLOGICAL OBSERVATIONS

GROUP 4: 15/10 MG BASE/KG/DAY

Animal: 776 (CONT.)
 Fetal Position: Right 05
 STERNUM
 (Skeletal) STERNEBRA(E), MALALIGNED AND FUSED - MALFORMATION; 4 AND 5 FUSED; 2, 4 AND 5 MALALIGNED MODERATE
 7TH STERNEBRA, PRESENT - VARIATION
 Unique Fetal Id.: 9

VERTEBRAL COLUMN
 (Skeletal) VERTEBRAE/RIBS, ANOMALY - MALFORMATION; CERVICAL CENTRA 1 THROUGH 3 MALFORMED, VENTRAL ASPECT OF LEFT CERVICAL ARCH 7 AND LEFT THORACIC ARCH 1 MALFORMED, LEFT RIB 1 ABSENT, VERTEBRAE THORACIC 8 THROUGH 12 AND LUMBAR 1 THROUGH 4 MALFORMED, FUSED, ABSENT OR ADDITIONAL; RIBS 8 THROUGH 12 BILATERAL, BENT, FUSED OR FORKED

Fetal Position: Right 06
 THORACIC CAVITY
 (Visceral) HEART, MAJOR BLOOD VESSEL, VARIATION - VARIATION; LEFT CAROTID ARISES FROM THE BRACHIOCEPHALIC TRUNK
 Unique Fetal Id.: 10

STERNUM
 (Skeletal) STERNEBRA(E), MALALIGNED, SLIGHT TO MODERATE - VARIATION; 4 AND 5, SLIGHT

Fetal Position: Right 07
 THORACIC CAVITY
 (Visceral) HEART, MAJOR BLOOD VESSEL, VARIATION - VARIATION; LEFT CAROTID ARISES FROM THE BRACHIOCEPHALIC TRUNK
 Unique Fetal Id.: 11

RIBS
 (Skeletal) RIB 13, FULL - VARIATION; BILATERAL

Fetal Position: Right 08
 VERTEBRAL COLUMN
 (Skeletal) VERTEBRAE, 27 PRESACRAL VERTEBRAE - VARIATION
 VERTEBRAE, 8 CERVICAL VERTEBRAE - MALFORMATION; RIGHT 8TH CERVICAL RIB PRESENT
 Unique Fetal Id.: 12

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INDIVIDUAL FETAL MORPHOLOGICAL OBSERVATIONS

GROUP 4: 15/10 MG BASE/KG/DAY

Animal: 777			
Fetal Position: Left 02		Unique Fetal Id.: 2	
SKULL			
(Skeletal) HYOID ARCH(ES), BENT - VARIATION; RIGHT, SLIGHT			
Animal: 778			
Fetal Position: Left 02		Unique Fetal Id.: 2	
RIBS			
(Skeletal) RIB 13, FULL - VARIATION; BILATERAL			
VERTEBRAL COLUMN			
(Skeletal) VERTEBRAE, 27 PRESACRAL VERTEBRAE - VARIATION			
Fetal Position: Right 01		Unique Fetal Id.: 4	
RIBS			
(Skeletal) RIB 13, FULL - VARIATION; BILATERAL			
Fetal Position: Right 03		Unique Fetal Id.: 6	
RIBS			
(Skeletal) RIB 13, RUDIMENTARY - VARIATION; RIGHT			
STERNUM			
(Skeletal) STERNEBRA(E), MALALIGNED, SLIGHT TO MODERATE - VARIATION; 5, SLIGHT			
Animal: 779			
Fetal Position: Left 03		Unique Fetal Id.: 3	
STERNUM			
(Skeletal) STERNEBRA(E), MALALIGNED, SLIGHT TO MODERATE - VARIATION; 4 AND 5, SLIGHT			
SKULL			
(Skeletal) HYOID ARCH(ES), BENT - VARIATION; LEFT MODERATE, RIGHT SLIGHT			

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INDIVIDUAL FETAL MORPHOLOGICAL OBSERVATIONS

GROUP 4: 15/10 MG BASE/KG/DAY

Animal: 779 (CONT.)		
Fetal Position: Right 01		Unique Fetal Id.: 5
STERNUM		
(Skeletal) STERNEBRA(E), 5-6, UNOSSIFIED	- VARIATION;	6 ONLY
Fetal Position: Right 02		Unique Fetal Id.: 6
STERNUM		
(Skeletal) STERNEBRA(E), 5-6, UNOSSIFIED	- VARIATION;	5 ONLY
Fetal Position: Right 03		Unique Fetal Id.: 7
RIBS		
(Skeletal) RIB 13, RUDIMENTARY	- VARIATION; BILATERAL (LEFT--NO ARTICULATING HEAD)	
Animal: 780		
Fetal Position: Left 02		Unique Fetal Id.: 2
RIBS		
(Skeletal) RIB 13, RUDIMENTARY	- VARIATION; BILATERAL (LEFT--NO ARTICULATING HEAD)	
Fetal Position: Right 02		Unique Fetal Id.: 4
THORACIC CAVITY		
(Visceral)	HEART, MAJOR BLOOD VESSEL, VARIATION - VARIATION; LEFT	
	CAROTID ARISES FROM THE BRACHIOCEPHALIC TRUNK	
STERNUM		
(Skeletal) STERNEBRA(E), 5-6, UNOSSIFIED	- VARIATION;	5 ONLY
Fetal Position: Right 03		Unique Fetal Id.: 5
RIBS		
(Skeletal) RIB 13, RUDIMENTARY	- VARIATION; LEFT	
Fetal Position: Right 04		Unique Fetal Id.: 6
THORACIC CAVITY		
(Visceral)	HEART, MAJOR BLOOD VESSEL, VARIATION - VARIATION; LEFT	
	CAROTID ARISES FROM THE BRACHIOCEPHALIC TRUNK	
RIBS		
(Skeletal) RIB 13, FULL - VARIATION;	LEFT FULL, RIGHT RUDIMENTARY	

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INDIVIDUAL FETAL MORPHOLOGICAL OBSERVATIONS

GROUP 4: 15/10 MG BASE/KG/DAY

Animal: 780 (CONT.)

Fetal Position: Right 05

STERNUM

Unique Fetal Id.: 7

(Skeletal) STERNEBRA(E), MALALIGNED, SLIGHT TO MODERATE - VARIATION;
2, 3 AND 4, SLIGHT

STERNEBRA(E), 5-6, UNOSSIFIED - VARIATION; 5 ONLY

Fetal Position: Right 06

RIBS

Unique Fetal Id.: 8

(Skeletal) RIB 13, FULL - VARIATION; LEFT RUDIMENTARY, RIGHT FULL

STERNUM

(Skeletal) STERNEBRA(E), MALALIGNED, SLIGHT TO MODERATE - VARIATION;
2-5, SLIGHT

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INDIVIDUAL FETAL MORPHOLOGICAL OBSERVATIONS

GROUP 5: 300 MG/KG/DAY (RETINOL PALMITATE)

Animal: 781		
Fetal Position: Left 01		Unique Fetal Id.: 1
RIBS		
(Skeletal) RIB 13, FULL - VARIATION; BILATERAL		
STERNUM		
(Skeletal) STERNEBRA(E), MALALIGNED, SLIGHT TO MODERATE - VARIATION; 2 AND 3, SLIGHT		
VERTEBRAL COLUMN		
(Skeletal) VERTEBRAE, 27 PRESACRAL VERTEBRAE - VARIATION		
HINDLIMBS		
(Skeletal) TALUS, UNOSSIFIED - VARIATION; BILATERAL		
ABDOMEN		
(Visceral) GALL BLADDER, VARIATION - VARIATION; SMALL		
Fetal Position: Left 02		Unique Fetal Id.: 2
RIBS		
(Skeletal) RIB 13, FULL - VARIATION; BILATERAL		
VERTEBRAL COLUMN		
(Skeletal) VERTEBRAE, 27 PRESACRAL VERTEBRAE - VARIATION		
Fetal Position: Left 03		Unique Fetal Id.: 3
RIBS		
(Skeletal) RIB 13, RUDIMENTARY - VARIATION; LEFT (NO ARTICULATING HEAD)		
VERTEBRAL COLUMN		
(Skeletal) VERTEBRAE, 27 PRESACRAL VERTEBRAE - VARIATION		
Fetal Position: Left 04		Unique Fetal Id.: 4
SKULL		
(Skeletal) HYOID, ANOMALY - MALFORMATION; ARCHES MALPOSITIONED		

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UIC/TRL STUDY NO. 173 DEVELOPMENTAL TOXICITY STUDY OF WR6026 DIHYDROCHLORIDE IN RABBITS

INDIVIDUAL FETAL MORPHOLOGICAL OBSERVATIONS

GROUP 5: 300 MG/KG/DAY (RETINOL PALMITATE)

Animal: 781 (CONT.)

Fetal Position: Left 06

THORACIC CAVITY

(Visceral) HEART, MAJOR BLOOD VESSEL, VARIATION - VARIATION; LEFT CAROTID ARISES FROM THE BRACHIOCEPHALIC TRUNK

Unique Fetal Id.: 6

Fetal Position: Left 07

RIBS

(Skeletal) RIB 13, FULL - VARIATION; BILATERAL

Unique Fetal Id.: 7

SKULL

(Skeletal) SKULL, ANOMALY - MALFORMATION; SUPRAOCCIPITAL FORMED IN TWO PIECES

HYOID, ANOMALY - MALFORMATION; RIGHT ARCH ABSENT/UNOSSIFIED, LEFT ARCH MALPOSITIONED

HEAD

(External) FACE, FACIAL BLEB(S) - MALFORMATION

Fetal Position: Right 01

RIBS

(Skeletal) RIB 13, FULL - VARIATION; BILATERAL

Unique Fetal Id.: 8

VERTEBRAL COLUMN

(Skeletal) VERTEBRAE, 27 PRESACRAL VERTEBRAE - VARIATION

Fetal Position: Right 03

RIBS

(Skeletal) RIB 13, RUDIMENTARY - VARIATION; LEFT (NO ARTICULATING HEAD)

Unique Fetal Id.: 10

Fetal Position: Right 04

NECK

(Visceral) THYROID, VARIATION - VARIATION; BILATERAL, REDDENED

Unique Fetal Id.: 11

RIBS

(Skeletal) RIB 13, FULL - VARIATION; BILATERAL

VERTEBRAL COLUMN

(Skeletal) VERTEBRAE, 27 PRESACRAL VERTEBRAE - VARIATION

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UIC/TRL STUDY NO. 173 DEVELOPMENTAL TOXICITY STUDY OF WR6026 DIHYDROCHLORIDE IN RABBITS

INDIVIDUAL FETAL MORPHOLOGICAL OBSERVATIONS

GROUP 5: 300 MG/KG/DAY (RETINOL PALMITATE)

Animal: 781 (CONT.)

Fetal Position: Right 05

THORACIC CAVITY

(Visceral) HEART, HEART AND/OR GREAT VESSEL, ANOMALY - MALFORMATION;

TRANSPOSITION OF THE GREAT VESSELS, BULBOUS ASCENDING AORTA, COARCTATION OF THE AORTIC ARCH

Unique Fetal Id.: 12

VERTEBRAL COLUMN

(Skeletal) VERTEBRAE, 27 PRESACRAL VERTEBRAE - VARIATION

SKULL

(Skeletal) SKULL, ANOMALY - MALFORMATION; SUPRAOCCIPITAL MALFORMED

ABDOMEN

(Visceral) URETER(S), RETROCAVAL - VARIATION; RIGHT

Fetal Position: Right 06

RIBS

(Skeletal) RIB 13, FULL - VARIATION; BILATERAL

Unique Fetal Id.: 13

VERTEBRAL COLUMN

(Skeletal) VERTEBRAE, 27 PRESACRAL VERTEBRAE - VARIATION

ABDOMEN

(Visceral) KIDNEY(S) AND/OR URETER(S), ANOMALY - MALFORMATION; KIDNEY, LEFT, RENAL PELVIS APPEARS MALFORMED

Animal: 782

Fetal Position: Left 02 *

RIBS

(Skeletal) RIB 13, RUDIMENTARY - VARIATION; RIGHT

7TH CERVICAL RIB, PRESENT - VARIATION; RIGHT

Unique Fetal Id.: 2

STERNUM

(Skeletal) STERNEBRA(E), MALALIGNED, SLIGHT TO MODERATE - VARIATION; 3, 4 AND 5, SLIGHT

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INDIVIDUAL FETAL MORPHOLOGICAL OBSERVATIONS

GROUP 5: 300 MG/KG/DAY (RETINOL PALMITATE)

Animal: 782 (CONT.)

Fetal Position: Left 02 (CONT.)

Unique Fetal Id.: 2

SKULL

(Skeletal) HYOID, ANOMALY - MALFORMATION; ARCHES ABSENT/UNOSSIFIED

TAIL

(External) TAIL, ANOMALY - MALFORMATION; SHORT

Comments: SKELETAL CONFIRMATION OF SHORT TAIL: CAUDAL VERTEBRAE MALFORMED OR ABSENT

Fetal Position: Left 03 *

Unique Fetal Id.: 3

RIBS

(Skeletal) RIB 13, FULL - VARIATION; BILATERAL

VERTEBRAL COLUMN

(Skeletal) VERTEBRAE, 27 PRESACRAL VERTEBRAE - VARIATION

SKULL

(Skeletal) SKULL, ANOMALY - MALFORMATION; JUGALS, SQUAMOSALS, PARIETALS MALFORMED
HYOID, ANOMALY - MALFORMATION; LEFT ARCH SMALL IN SIZE

TAIL

(External) TAIL, ANOMALY - MALFORMATION; SHORT

Comments: SKELETAL CONFIRMATION OF SHORT TAIL: CAUDAL VERTEBRAE MALFORMED, FUSED OR ABSENT

Fetal Position: Left 04 *

Unique Fetal Id.: 4

RIBS (Skeletal) 7TH CERVICAL RIB, PRESENT - VARIATION; LEFT

STERNUM (Skeletal) STERNEBRA(E), 5-6, UNOSSIFIED - VARIATION; 5 ONLY

SKULL (Skeletal) SKULL, ANOMALY - MALFORMATION; SQUAMOSALS MALFORMED

TAIL (External) TAIL, ANOMALY - MALFORMATION; SHORT

Comments: SKELETAL CONFIRMATION OF SHORT TAIL: CAUDAL VERTEBRAE MALFORMED, FUSED OR ABSENT

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UIC/TRL STUDY NO. 173 DEVELOPMENTAL TOXICITY STUDY OF WR6026 DIHYDROCHLORIDE IN RABBITS

INDIVIDUAL FETAL MORPHOLOGICAL OBSERVATIONS

GROUP 5: 300 MG/KG/DAY (RETINOL PALMITATE)

Animal: 782 (CONT.)

Fetal Position: Left 05 *

RIBS

Unique Fetal Id.: 5

(Skeletal) RIB 13, FULL - VARIATION; LEFT RUDIMENTARY, RIGHT FULL

VERTEBRAL COLUMN

(Skeletal) VERTEBRAE, 27 PRESACRAL VERTEBRAE - VARIATION

SKULL

(Skeletal) SKULL, ANOMALY - MALFORMATION; JUGALS, SQUAMOSALS, PARIETALS MALFORMED

TAIL

(External) TAIL, ANOMALY - MALFORMATION; SHORT

HEAD

(External) FACE, FACIAL BLEB(S) - MALFORMATION

Comments: SKELETAL CONFIRMATION OF SHORT TAIL: CAUDAL VERTEBRAE MALFORMED, FUSED OR ABSENT

Fetal Position: Right 03 *

THORACIC CAVITY

Unique Fetal Id.: 9

(Visceral) HEART, MAJOR BLOOD VESSEL, VARIATION - VARIATION; LEFT CAROTID ARISES FROM BRACHIOCEPHALIC TRUNK

RIBS

(Skeletal) RIB 13, FULL - VARIATION; LEFT FULL, RIGHT RUDIMENTARY

VERTEBRAL COLUMN

(Skeletal) VERTEBRAE, 27 PRESACRAL VERTEBRAE - VARIATION

SKULL

(Skeletal) SKULL, ANOMALY - MALFORMATION; SQUAMOSALS, PARIETALS MALFORMED

TAIL

(External) TAIL, ANOMALY - MALFORMATION; SHORT

Comments: SKELETAL CONFIRMATION OF SHORT TAIL: CAUDAL VERTEBRAE MALFORMED OR ABSENT

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UIC/TRL STUDY NO. 173 DEVELOPMENTAL TOXICITY STUDY OF WR6026 DIHYDROCHLORIDE IN RABBITS

INDIVIDUAL FETAL MORPHOLOGICAL OBSERVATIONS

GROUP 5: 300 MG/KG/DAY (RETINOL PALMITATE)

Animal: 783

Fetal Position: Left 02 *
THORACIC CAVITY

Unique Fetal Id.: 2

(Visceral) HEART, MAJOR BLOOD VESSEL, VARIATION - VARIATION; ACCESSORY LEFT SUBCLAVIAN

VERTEBRAL COLUMN

(Skeletal) CAUDAL VERTEBRAE, ANOMALY - MALFORMATION; CAUDAL VERTEBRAE MALPOSITIONED OR FUSED

SKULL

(Skeletal) HYOID, ANOMALY - MALFORMATION; ARCHES MALPOSITIONED

HEAD

(External) HEAD, MICROCEPHALY - MALFORMATION
FACE, FACIAL BLEB(S) - MALFORMATION; BILATERAL

Comments: SKELETAL CONFIRMATION OF MICROCEPHALY: SKULL BONES MALFORMED

Fetal Position: Right 01 *

Unique Fetal Id.: 3

VERTEBRAL COLUMN
(Skeletal)

VERTEBRAE, 25 PRESACRAL VERTEBRAE - VARIATION
CAUDAL VERTEBRAE, ANOMALY - MALFORMATION; CAUDAL VERTEBRAE MALFORMED OR FUSED

SKULL

(Skeletal) HYOID, ANOMALY - MALFORMATION; ARCHES ABSENT OR UNOSSIFIED

HEAD

(External) HEAD, MICROCEPHALY - MALFORMATION
JAW, MAXILLAE, MICROGNATHIA - MALFORMATION
FACE, FACIAL BLEB(S) - MALFORMATION; BILATERAL

Comments: SKELETAL CONFIRMATION OF MAXILLAE MICROGNATHIA AND MICROCEPHALY: SKULL BONES MALFORMED

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INDIVIDUAL FETAL MORPHOLOGICAL OBSERVATIONS

GROUP 5: 300 MG/KG/DAY (RETINOL PALMITATE)

Animal: 783 (CONT.)	Unique Fetal Id.: 4
Fetal Position: Right 02	
STERNUM	
(Skeletal) STERNEBRA(E), 5-6, UNOSSIFIED - VARIATION; 5 ONLY	
SKULL	
(Skeletal) HYOID, ANOMALY - MALFORMATION; ARCHES UNOSSIFIED/ABSENT	
TAIL	
(External) TAIL, ANOMALY - MALFORMATION; SHORT	
ABDOMEN	
(Visceral) URETER(S), RETROCAVAL - VARIATION	
KIDNEY(S) AND/OR URETER(S), ANOMALY - MALFORMATION; LEFT KIDNEY, MALFORMED, VERY SMALL IN SIZE	
HEAD	
(External) HEAD, MICROCEPHALY - MALFORMATION	
FACE, FACIAL BLEB(S) - MALFORMATION; BILATERAL	
Fetal Position: Right 03 *	Unique Fetal Id.: 5
STERNUM	
(Skeletal) STERNEBRA(E), MALALIGNED, SLIGHT TO MODERATE - VARIATION; 4, 5 AND 6, SLIGHT	
SKULL	
(Skeletal) SKULL, ANOMALY - MALFORMATION; SUPRAOCCIPITAL, SQUAMOSALS, JUGALS, MAXILLAE MALFORMED	
HYOID, ANOMALY - MALFORMATION; ARCHES UNOSSIFIED/ABSENT	
TAIL	
(External) TAIL, ANOMALY - MALFORMATION; BENT	
HEAD	
(External) FACE, FACIAL BLEB(S) - MALFORMATION; BILATERAL	
Comments: SKELETAL CONFIRMATION OF BENT TAIL: CAUDAL VERTEBRAE MALFORMED/FUSED	

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UIC/TRL STUDY NO. 173 DEVELOPMENTAL TOXICITY STUDY OF WR6026 DIHYDROCHLORIDE IN RABBITS

INDIVIDUAL FETAL MORPHOLOGICAL OBSERVATIONS

GROUP 5: 300 MG/KG/DAY (RETINOL PALMITATE)

Animal: 783 (CONT.) Unique Fetal Id.: 6
Fetal Position: Right 04 *
STERNUM (Skeletal) STERNEBRA(E), MALALIGNED, SLIGHT TO MODERATE - VARIATION; 5, SLIGHT VERTEBRAL COLUMN
(Skeletal) CAUDAL VERTEBRAE, ANOMALY - MALFORMATION; DISTAL CAUDAL VERTEBRAE MALFORMED/FUSED
SKULL (Skeletal) HYOID, ANOMALY - MALFORMATION; ARCHES ABSENT/UNOSSIFIED
HEAD (External) HEAD, MICROCEPHALY - MALFORMATION
FACE, FACIAL BLEB(S) - MALFORMATION; BILATERAL
Comments: SKELETAL CONFIRMATION OF MICROCEPHALY: SKULL BONES MALFORMED
Fetal Position: Right 05 * Unique Fetal Id.: 7
THORACIC CAVITY (Visceral) HEART, MAJOR BLOOD VESSEL, VARIATION - VARIATION; LEFT CAROTID ARISES FROM BRACHIOCEPHALIC TRUNK
STERNUM (Skeletal) STERNEBRA(E), 5-6, UNOSSIFIED - VARIATION; 5 ONLY
SKULL (Skeletal) SKULL, ANOMALY - MALFORMATION; SQUAMOSALS, JUGALS MALFORMED
HYOID, ANOMALY - MALFORMATION; ARCHES ABSENT/UNOSSIFIED
TAIL (External) TAIL, ANOMALY - MALFORMATION; BENT
ABDOMEN (Visceral) KIDNEY(S) AND/OR URETER(S), ANOMALY - MALFORMATION; KIDNEY, LEFT MALFORMED, MISSHAPENED AND UNASCENDED
HEAD (External) FACE, FACIAL BLEB(S) - MALFORMATION; BILATERAL
Comments: SKELETAL CONFIRMATION OF BENT TAIL: CAUDAL VERTEBRAE MALFORMED

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INDIVIDUAL FETAL MORPHOLOGICAL OBSERVATIONS

GROUP 5: 300 MG/KG/DAY (RETINOL PALMITATE)

Animal: 783 (CONT.)
 Fetal Position: Right 06 * Unique Fetal Id.: 8
 STERNUM
 (Skeletal) STERNEBRA(E), 5-6, UNOSSIFIED - VARIATION; 5 ONLY
 SKULL
 (Skeletal) HYOID, ANOMALY - MALFORMATION; ARCHES ABSENT/UNOSSIFIED
 PALATE, CLEFT PALATE - MALFORMATION

TAIL
 (External) TAIL, ANOMALY - MALFORMATION; BENT

HEAD
 (External) HEAD, MICROCEPHALY - MALFORMATION
 FACE, FACIAL BLEB(S) - MALFORMATION; BILATERAL

Comments: SKELETAL CONFIRMATION OF EXTERNAL FINDINGS: BENT TAIL--DISTAL CAUDAL VERTEBRAE MALFORMED;
 MICROCEPHALY--SKULL BONES MALFORMED

Fetal Position: Right 07 * Unique Fetal Id.: 9

STERNUM
 (Skeletal) STERNEBRA(E), MALALIGNED, SLIGHT TO MODERATE - VARIATION;
 4, SLIGHT
 STERNEBRA(E), 5-6, UNOSSIFIED - VARIATION; 5 ONLY

SKULL
 (Skeletal) HYOID, ANOMALY - MALFORMATION; ARCHES UNOSSIFIED/ABSENT, BODY MALFORMED

TAIL
 (External) TAIL, ANOMALY - MALFORMATION; BENT, SHORT

HEAD
 (External) HEAD, MICROCEPHALY - MALFORMATION
 FACE, FACIAL BLEB(S) - MALFORMATION; BILATERAL

Comments: SKELETAL CONFIRMATION OF EXTERNAL FINDINGS: SHORT, BENT TAIL--CAUDAL VERTEBRAE MALFORMED/FUSED;
 MICROCEPHALY--SKULL BONES MALFORMED

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UIC/TRL STUDY NO. 173 DEVELOPMENTAL TOXICITY STUDY OF WR6026 DIHYDROCHLORIDE IN RABBITS

INDIVIDUAL FETAL MORPHOLOGICAL OBSERVATIONS

GROUP 5: 300 MG/KG/DAY (RETINOL PALMITATE)

Animal: 784
 Fetal Position: Left 01 * Unique Fetal Id.: 1
 SKULL (Skeletal) SKULL, ANOMALY - MALFORMATION; SQUAMOSALS, PARIETALS, SUPRAOCCIPITAL MALFORMED
 HYOID, ANOMALY - MALFORMATION; LEFT ARCH ABSENT/UNOSSIFIED

Fetal Position: Right 01 * Unique Fetal Id.: 2
 SKULL (Skeletal) SKULL, ANOMALY - MALFORMATION; SQUAMOSALS FUSED TO PARIETALS
 HYOID, ANOMALY - MALFORMATION; ARCHES MALFORMED

TAIL (External) TAIL, ANOMALY - MALFORMATION; BENT

HEAD (External) PINNA(E), PINNA(E) ANOMALY - MALFORMATION; BILATERAL, SMALL IN SIZE AND MALPOSITIONED

Comments: SKELETAL CONFIRMATION OF BENT TAIL: CAUDAL VERTEBRAE MALFORMED

Fetal Position: Right 02 * Unique Fetal Id.: 3
 SKULL (Skeletal) SKULL, ANOMALY - MALFORMATION; SQUAMOSALS FUSED TO PARIETALS

Fetal Position: Right 03 * Unique Fetal Id.: 4
 SKULL (Skeletal) SKULL, ANOMALY - MALFORMATION; JUGALS, SQUAMOSALS, PARIETALS--FUSED/MALFORMED
 HYOID, ANOMALY - MALFORMATION; ARCHES MALPOSITIONED, BENT MODERATE

TAIL (External) TAIL, ANOMALY - MALFORMATION; ABSENT

HEAD (External) PINNA(E), PINNA(E) ANOMALY - MALFORMATION; BILATERAL, SMALL IN SIZE AND MALPOSITIONED

Comments: SKELETAL CONFIRMATION OF ABSENT TAIL: CAUDAL VERTEBRAE MALFORMED/ABSENT

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INDIVIDUAL FETAL MORPHOLOGICAL OBSERVATIONS

GROUP 5: 300 MG/KG/DAY (RETINOL PALMITATE)

Animal: 784 (CONT.)

Fetal Position: Right 04 *

Unique Fetal Id.: 5

STERNUM

(Skeletal) STERNEBRA(E), 5-6, UNOSSIFIED - VARIATION; 5 ONLY

SKULL

(Skeletal) SKULL, ANOMALY - MALFORMATION; JUGALS MALFORMED
HYOID, ANOMALY - MALFORMATION; LEFT ARCH ABSENT/UNOSSIFIED

TAIL

(External) TAIL, ANOMALY - MALFORMATION; SHORT

ABDOMEN

(visceral) GALL BLADDER, VARIATION - VARIATION; SMALL IN SIZE
KIDNEY(S) AND/OR URETER(S), ANOMALY - MALFORMATION; KIDNEY
- RIGHT, MALFORMED, SMALL IN SIZE, UNASCENDED

HEAD

(External) PINNA(E), PINNA(E) ANOMALY - MALFORMATION; BILATERAL,
SMALL IN SIZE AND MALPOSITIONED; LEFT, MALFORMED

Comments: SKELETAL CONFIRMATION OF SHORT TAIL: SOME CAUDAL VERTEBRAE ABSENT

Fetal Position: Right 05 *

Unique Fetal Id.: 6

SKULL

(Skeletal) SKULL, ANOMALY - MALFORMATION; SUPRAOCCIPITAL, SQUAMOSALS, PARIETALS MALFORMED
HYOID, ANOMALY - MALFORMATION; LEFT ARCH ABSENT/UNOSSIFIED

Fetal Position: Right 06 *

Unique Fetal Id.: 7

SKULL

(Skeletal) SKULL, ANOMALY - MALFORMATION; JUGALS, SQUAMOSALS, PARIETALS, SUPRAOCCIPITAL MALFORMED

TAIL

(External) TAIL, ANOMALY - MALFORMATION; SHORT

Comments: SKELETAL CONFIRMATION OF SHORT TAIL: SOME CAUDAL VERTEBRAE ABSENT

APPENDIX D

UIC/TRL STUDY NO. 173 DEVELOPMENTAL TOXICITY STUDY OF WR6026 DIHYDROCHLORIDE IN RABBITS

INDIVIDUAL FETAL MORPHOLOGICAL OBSERVATIONS

GROUP 5: 300 MG/KG/DAY (RETINOL PALMITATE)

Animal: 784 (CONT.)	Unique Fetal Id.: 8
Fetal Position: Right 07 *	
NECK	
(Visceral) THYROID, VARIATION - VARIATION; BILATERAL, REDDENED	
THORACIC CAVITY	
(Visceral) HEART, MAJOR BLOOD VESSEL, VARIATION - VARIATION; LEFT CAROTID ARISES FROM BRACHIOCEPHALIC TRUNK	
SKULL	
(Skeletal) SKULL, ANOMALY - MALFORMATION; JUGALS, SQUAMOSALS, PARIETALS, INTERPARIETAL, SUPRAOCCIPITAL MALFORMED	
HYOID, ANOMALY - MALFORMATION; ARCHES ABSENT/UNOSSIFIED	
ABDOMEN	
(Visceral) GALL BLADDER, VARIATION - VARIATION; SMALL IN SIZE	
Fetal Position: Right 08 *	Unique Fetal Id.: 9
RIBS	
(Skeletal) RIB 13, RUDIMENTARY - VARIATION; RIGHT	
STERNUM	
(Skeletal) STERNEBRA(E), MALALIGNED, SLIGHT TO MODERATE - VARIATION; 3 AND 4, SLIGHT STERNEBRA(E), 5-6, UNOSSIFIED - VARIATION; 5 ONLY	
VERTEBRAL COLUMN	
(Skeletal) VERTEBRAE, 27 PRESACRAL VERTEBRAE - VARIATION	
SKULL	
(Skeletal) SKULL, ANOMALY - MALFORMATION; SQUAMOSALS, PARIETALS, SUPRAOCCIPITAL MALFORMED	
HYOID, ANOMALY - MALFORMATION; ARCHES ABSENT/UNOSSIFIED	
TAIL	
(External) TAIL, ANOMALY - MALFORMATION; ABSENT	
HEAD	
(External) PINNA(E), PINNA(E) ANOMALY - MALFORMATION; SMALL IN SIZE AND MALPOSITIONED	

Comments: SKELETAL CONFIRMATION OF ABSENT TAIL: CAUDAL VERTEBRAE MALFORMED/ABSENT AND MALPOSITIONED

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UIC/TRL STUDY NO. 173 DEVELOPMENTAL TOXICITY STUDY OF WR6026 DIHYDROCHLORIDE IN RABBITS

INDIVIDUAL FETAL MORPHOLOGICAL OBSERVATIONS

GROUP 5: 300 MG/KG/DAY (RETINOL PALMITATE)

Animal: 785		Unique Fetal Id.: 1
Fetal Position: Left 01		
RIBS	(Skeletal) RIB 13, FULL - VARIATION; LEFT	
SKULL	(Skeletal) SKULL, ANOMALY - MALFORMATION; SQUAMOSALS FUSED TO PARIETALS	
ABDOMEN	(Visceral) URETER(S), RETROCAVAL - VARIATION; RIGHT	
Fetal Position: Left 02		Unique Fetal Id.: 2
STERNUM	(Skeletal) STERNEBRA(E), 5-6, UNOSSIFIED - VARIATION; 5 ONLY	
SKULL	(Skeletal) SKULL, ANOMALY - MALFORMATION; JUGALS, SQUAMOSALS, PARIETALS MALFORMED HYOID, ANOMALY - MALFORMATION; ARCHES ABSENT/UNOSSIFIED, BODY MALFORMED	
Fetal Position: Left 03		Unique Fetal Id.: 3
RIBS	(Skeletal) 7TH CERVICAL RIB, PRESENT - VARIATION; BILATERAL	
STERNUM	(Skeletal) STERNEBRA(E), 5-6, UNOSSIFIED - VARIATION; 6 ONLY	
SKULL	(Skeletal) SKULL, ANOMALY - MALFORMATION; JUGALS, SQUAMOSALS, PARIETALS MALFORMED	
HEAD	(External) FACE, FACIAL BLEB(S) - MALFORMATION; RIGHT	
Fetal Position: Left 04		Unique Fetal Id.: 4
SKULL	(Skeletal) SKULL, ANOMALY - MALFORMATION; MAXILLAE, JUGALS, SQUAMOSALS MALFORMED HYOID, ANOMALY - MALFORMATION; ARCHES ABSENT/UNOSSIFIED	
HEAD	(External) FACE, FACIAL BLEB(S) - MALFORMATION; BILATERAL	

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INDIVIDUAL FETAL MORPHOLOGICAL OBSERVATIONS

GROUP 5: 300 MG/KG/DAY (RETINOL PALMITATE)

Animal: 785 (CONT.)	Unique Fetal Id.: 5
Fetal Position: Left 05	
SKULL	
(Skeletal) HYOID, ANOMALY - MALFORMATION; RIGHT ARCH ABSENT/UNOSSIFIED	
Fetal Position: Right 02	Unique Fetal Id.: 7
RIBS	
(Skeletal) RIB 13, FULL - VARIATION; LEFT FULL, RIGHT RUDIMENTARY (NO ARTICULATING HEAD)	
SKULL	
(Skeletal) SKULL, ANOMALY - MALFORMATION; MAXILLAE, MANDIBLES, JUGALS, SQUAMOSALS, PARIETALS MALFORMED	
HEAD	
(External) HEAD, FLESHY PROTUBERANCE - MALFORMATION; RIGHT SIDE	
Fetal Position: Right 03	Unique Fetal Id.: 8
RIBS	
(Skeletal) RIB 13, RUDIMENTARY - VARIATION; RIGHT	
VERTEBRAL COLUMN	
(Skeletal) CAUDAL VERTEBRAE, ANOMALY - MALFORMATION; MALFORMED	
SKULL	
(Skeletal) SKULL, ANOMALY - MALFORMATION; JUGALS, SQUAMOSALS, PARIETALS MALFORMED	
HYOID, ANOMALY - MALFORMATION; ARCHES MALPOSITIONED	
HEAD	
(External) FACE, FACIAL BLEB(S) - MALFORMATION; BILATERAL	
Fetal Position: Right 04	Unique Fetal Id.: 9
TAIL	
(External) TAIL, ANOMALY - MALFORMATION; SHORT	
Comments: SKELETAL CONFIRMATION OF SHORT TAIL: SOME CAUDAL VERTEBRAE MALFORMED OR ABSENT	

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UIC/TRL STUDY NO. 173 DEVELOPMENTAL TOXICITY STUDY OF WR6026 DIHYDROCHLORIDE IN RABBITS

INDIVIDUAL FETAL MORPHOLOGICAL OBSERVATIONS

GROUP 5: 300 MG/KG/DAY (RETINOL PALMITATE)

Animal: 786
Fetal Position: Right 02 * Unique Fetal Id.: 6
ANUS (External) ANUS, ANAL ATRESIA - MALFORMATION

RIBS (Skeletal) RIB 13, FULL - VARIATION; BILATERAL

VERTEBRAL COLUMN (Skeletal) VERTEBRAE, 27 PRESACRAL VERTEBRAE - VARIATION; 27TH--ARCHES ONLY

SKULL (Skeletal) HYOID, ANOMALY - MALFORMATION; ARCHES ABSENT/UNOSSIFIED

TAIL (External) TAIL, ANOMALY - MALFORMATION; ABSENT

ABDOMEN (Visceral) GALL BLADDER, VARIATION - VARIATION; ABSENT
KIDNEY(S) AND/OR URETER(S), ANOMALY - MALFORMATION; LEFT
KIDNEY AND URETER ABSENT, RIGHT KIDNEY SMALL, MALFORMED
AND UNASCENDED

HEAD (External) HEAD, MICROCEPHALY - MALFORMATION
PINNA(E), PINNA(E) ANOMALY - MALFORMATION; MALPOSITIONED,
MALFORMED AND SMALL IN SIZE
FACIAL PAPILLA(E), FACIAL PAPILLA(E) ANOMALY -
MALFORMATION; MALPOSITIONED
MOUTH, PALATE, CLEFT PALATE - MALFORMATION
JAW, MANDIBLE, MICROGNATHIA - MALFORMATION
FACE, FACIAL BLEB(S) - MALFORMATION; BILATERAL

Comments: SKELETAL CONFIRMATION OF EXTERNAL FINDINGS: MICROCEPHALY, MANDIBULAR MICROGNATHIA, AND CLEFT
PALATE--SKULL BONES MALFORMED; TAIL ABSENT--SACRAL VERTEBRAE MALFORMED, ALL CAUDAL VERTEBRAE ABSENT

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UIC/TRL STUDY NO. 173 DEVELOPMENTAL TOXICITY STUDY OF WR6026 DIHYDROCHLORIDE IN RABBITS

INDIVIDUAL FETAL MORPHOLOGICAL OBSERVATIONS

GROUP 5: 300 MG/KG/DAY (RETINOL PALMITATE)

Animal: 787

Fetal Position: Left 01 * Unique Fetal Id.: 1

VERTEBRAL COLUMN

(Skeletal) VERTEBRAE, 27 PRESACRAL VERTEBRAE - VARIATION

SKULL

(Skeletal) SKULL, ANOMALY - MALFORMATION; JUGALS, SQUAMOSALS MALFORMED
HYOID, ANOMALY - MALFORMATION; ARCHES ABSENT/UNOSSIFIED, BODY MALFORMED

TAIL

(External) TAIL, ANOMALY - MALFORMATION; SHORT

HEAD

(External) PINNA(E), PINNA(E) ANOMALY - MALFORMATION; BILATERAL, SMALL IN SIZE AND MALPOSITIONED
FACE, FACIAL BLEB(S) - MALFORMATION; LEFT

Comments: SKELETAL CONFIRMATION OF SHORT TAIL: SOME CAUDAL VERTEBRAE ABSENT/MALFORMED

Fetal Position: Left 03 *

Unique Fetal Id.: 3

RIBS

(Skeletal) RIB 13, FULL - VARIATION; RIGHT

VERTEBRAL COLUMN

(Skeletal) VERTEBRAE, 27 PRESACRAL VERTEBRAE - VARIATION

TAIL

(External) TAIL, ANOMALY - MALFORMATION; BENT

Comments: SKELETAL CONFIRMATION OF BENT TAIL: ONE CAUDAL VERTEBRA MALPOSITIONED

Fetal Position: Right 01

Unique Fetal Id.: 4

SKULL

(Skeletal) SKULL, ANOMALY - MALFORMATION; SQUAMOSALS FUSED TO PARIETALS
HYOID, ANOMALY - MALFORMATION; LEFT ARCH MALPOSITIONED,
RIGHT ARCH ABSENT/UNOSSIFIED

APPENDIX D

UIC/TRL STUDY NO. 173 DEVELOPMENTAL TOXICITY STUDY OF WR6026 DIHYDROCHLORIDE IN RABBITS
INDIVIDUAL FETAL MORPHOLOGICAL OBSERVATIONS

GROUP 5: 300 MG/KG/DAY (RETINOL PALMITATE)

Animal: 787 (CONT.)	Unique Fetal Id.: 5
Fetal Position: Right 02	
STERNUM	
(Skeletal) STERNEBRA(E), MALALIGNED, SLIGHT TO MODERATE - VARIATION; 3, 4 AND 6, SLIGHT	
VERTEBRAL COLUMN	
(Skeletal) CAUDAL VERTEBRAE, ANOMALY - MALFORMATION; CAUDAL VERTEBRA MALPOSITIONED	
SKULL	
(Skeletal) SKULL, ANOMALY - MALFORMATION; SQUAMOSALS MALFORMED	
HYOID, ANOMALY - MALFORMATION; ARCHES SMALL	
Fetal Position: Right 04 *	Unique Fetal Id.: 7
THORACIC CAVITY	
(Visceral) HEART, MAJOR BLOOD VESSEL, VARIATION - VARIATION; RETROESOPHAGEAL RIGHT SUBCLAVIAN	
RIBS	
(Skeletal) 7TH CERVICAL RIB, PRESENT - VARIATION; RIGHT	
STERNUM	
(Skeletal) STERNEBRA(E), MALALIGNED, SLIGHT TO MODERATE - VARIATION; 3, 4 AND 5, SLIGHT	
SKULL	
(Skeletal) SKULL, ANOMALY - MALFORMATION; SQUAMOSALS MALFORMED	
HYOID, ANOMALY - MALFORMATION; ARCHES ABSENT/UNOSSIFIED, BODY MALFORMED	
TAIL	
(External) TAIL, ANOMALY - MALFORMATION; SHORT	
HEAD	
(External) PINNA(E), PINNA(E) ANOMALY - MALFORMATION; BILATERAL, SMALL IN SIZE	

Comments: SKELETAL CONFIRMATION OF SHORT TAIL: SOME CAUDAL VERTEBRAE ABSENT

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UIC/TRL STUDY NO. 173 DEVELOPMENTAL TOXICITY STUDY OF WR6026 DIHYDROCHLORIDE IN RABBITS

INDIVIDUAL FETAL MORPHOLOGICAL OBSERVATIONS

GROUP 5: 300 MG/KG/DAY (RETINOL PALMITATE)

Animal: 787 (CONT.)
Fetal Position: Right 05 * Unique Fetal Id.: 8
THORACIC CAVITY
(Visceral) HEART, HEART AND/OR GREAT VESSEL, ANOMALY - MALFORMATION;
INTERRUPTED AORTIC ARCH, INTERVENTRICULAR SEPTAL DEFECT
HEART, MAJOR BLOOD VESSEL, VARIATION - VARIATION; RIGHT
SUBCLAVIAN AND LEFT SUBCLAVIAN ARISE FROM PULMONARY TRUNK

RIBS
(Skeletal) 7TH CERVICAL RIB, PRESENT - VARIATION; BILATERAL

STERNUM
(Skeletal) STERNEBRA(E), FUSED - MALFORMATION; 1-5

VERTEBRAL COLUMN
(Skeletal) VERTEBRAE, 27 PRESACRAL VERTEBRAE - VARIATION

SKULL
(Skeletal) SKULL, ANOMALY - MALFORMATION; MAXILLAE, JUGALS, SQUAMOSALS MALFORMED
HYOID, ANOMALY - MALFORMATION; ARCHES SMALL

TAIL
(External) TAIL, ANOMALY - MALFORMATION; SHORT

HEAD
(External) PINNA(E), PINNA(E) ANOMALY - MALFORMATION; BILATERAL, SMALL IN SIZE

Comments: SKELETAL CONFIRMATION OF SHORT TAIL: CAUDAL VERTEBRAE SMALL

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UIC/TRL STUDY NO. 173 DEVELOPMENTAL TOXICITY STUDY OF WR6026 DIHYDROCHLORIDE IN RABBITS

INDIVIDUAL FETAL MORPHOLOGICAL OBSERVATIONS

GROUP 5: 300 MG/KG/DAY (RETINOL PALMITATE)

Animal: 789
Fetal Position: Left 02 * Unique Fetal Id.: 2
THORACIC CAVITY
(Visceral) HEART, HEART AND/OR GREAT VESSEL, ANOMALY - MALFORMATION;
AORTA--ENLARGED

RIBS (Skeletal) 7TH CERVICAL RIB, PRESENT - VARIATION; LEFT

STERNUM (Skeletal) STERNEBRA(E), 5-6, UNOSSIFIED - VARIATION; 5 ONLY

SKULL (Skeletal) HYOID, ANOMALY - MALFORMATION; ARCHES ABSENT/UNOSSIFIED

TAIL (External) TAIL, ANOMALY - MALFORMATION; SHORT

ABDOMEN (Visceral) KIDNEY(S) AND/OR URETER(S), ANOMALY - MALFORMATION; RIGHT
KIDNEY, MISPLACED, MALFORMED, UNASCENDED

HEAD (External) HEAD, MICROCEPHALY - MALFORMATION
MOUTH, MACROSTOMIA - MALFORMATION
FACE, FACIAL BLEB(S) - MALFORMATION; BILATERAL

Comments: SKELETAL CONFIRMATION OF EXTERNAL FINDINGS: SHORT TAIL--CAUDAL VERTEBRAE MALFORMED;
MICROCEPHALY--SKULL BONES MALFORMED

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UIC/TRL STUDY NO. 173 DEVELOPMENTAL TOXICITY STUDY OF WR6026 DIHYDROCHLORIDE IN RABBITS

INDIVIDUAL FETAL MORPHOLOGICAL OBSERVATIONS

GROUP 5: 300 MG/KG/DAY (RETINOL PALMITATE)

Animal: 789 (CONT.)	Unique Fetal Id.: 4
Fetal Position: Left 04	
RIBS	
(Skeletal) RIB 13, FULL - VARIATION; BILATERAL	
VERTEBRAL COLUMN	
(Skeletal) VERTEBRAE, 27 PRESACRAL VERTEBRAE - VARIATION	
SKULL	
(Skeletal) SKULL, ANOMALY - MALFORMATION; MAXILLAE, JUGALS, SQUAMOSALS MALFORMED	
HYOID, ANOMALY - MALFORMATION; BODY MALFORMED, LEFT ARCH MALFORMED, RIGHT ARCH BENT SLIGHT	
ABDOMEN	
(Visceral) KIDNEY(S), HYDRONEPHROSIS - VARIATION; BILATERAL	
URETER(S), DISTENDED - VARIATION; BILATERAL, SEVERE	
URETER(S), RETROCAVAL - VARIATION; RIGHT	
HEAD	
(External) MOUTH, MACROSTOMIA - MALFORMATION	
FACE, FACIAL BLEB(S) - MALFORMATION; BILATERAL	
Fetal Position: Right 02 *	Unique Fetal Id.: 6
RIBS	
(Skeletal) RIB 13, FULL - VARIATION; BILATERAL	
STERNUM	
(Skeletal) STERNEBRA(E), MALALIGNED, SLIGHT TO MODERATE - VARIATION; 2-5, SLIGHT	
VERTEBRAL COLUMN	
(Skeletal) VERTEBRAE, ANOMALY - MALFORMATION; 28 PRESACRAL VERTEBRAE	
SKULL	
(Skeletal) HYOID, ANOMALY - MALFORMATION; LEFT ARCH ABSENT/UNOSSIFIED	
PALATE, CLEFT PALATE - MALFORMATION	

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UIC/TRL STUDY NO. 173 DEVELOPMENTAL TOXICITY STUDY OF WR6026 DIHYDROCHLORIDE IN RABBITS
INDIVIDUAL FETAL MORPHOLOGICAL OBSERVATIONS

GROUP 5: 300 MG/KG/DAY (RETINOL PALMITATE)

Animal: 789 (CONT.)	Unique Fetal Id.: 6
Fetal Position: Right 02 (CONT.)	
TAIL	(External) TAIL, ANOMALY - MALFORMATION; SHORT
ABDOMEN	(Visceral) KIDNEY(S) AND/OR URETER(S), ANOMALY - MALFORMATION; RIGHT KIDNEY--MALFORMED, UNASCENDED, SMALL
HEAD	(External) HEAD, MICROCEPHALY - MALFORMATION PINNA(E), PINNA(E) ANOMALY - MALFORMATION; BILATERAL, SMALL IN SIZE AND MALPOSITIONED MOUTH, MACROSTOMIA - MALFORMATION JAW, MAXILLAE, MICROGNATHIA - MALFORMATION FACE, FACIAL BLEB(S) - MALFORMATION; BILATERAL
Comments:	SKELETAL CONFIRMATION OF EXTERNAL FINDINGS: SHORT TAIL--CAUDAL VERTEBRAE MALFORMED/ABSENT; MICROCEPHALY AND MAXILLAE MICROGNATHIA--SKULL BONES MALFORMED

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UIC/TRL STUDY NO. 173 DEVELOPMENTAL TOXICITY STUDY OF WR6026 DIHYDROCHLORIDE IN RABBITS

INDIVIDUAL FETAL MORPHOLOGICAL OBSERVATIONS

GROUP 5: 300 MG/KG/DAY (RETINOL PALMITATE)

Animal:	791	Unique Fetal Id.:	1
Fetal Position:	Left 01		
RIBS	(Skeletal) RIB 13, FULL - VARIATION; LEFT (SMALL ARTICULATING HEAD)		
STERNUM	(Skeletal) STERNEBRA(E), MALALIGNED, SLIGHT TO MODERATE - VARIATION; 4 and 5, SLIGHT		
SKULL	(Skeletal) SKULL, ANOMALY - MALFORMATION; LEFT SQUAMOSAL MALFORMED HYOID, ANOMALY - MALFORMATION; RIGHT ARCH ABSENT/UNOSSIFIED		
HEAD	(External) MOUTH, MACROSTOMIA - MALFORMATION MOUTH, TONGUE, MACROGLOSSIA - MALFORMATION FACE, FACIAL BLEB(S) - MALFORMATION; BILATERAL		
Fetal Position:	Left 02		
Late Resorption:	Crown-Rump Length: 50 mm		
Fetal Position:	Left 03 *	Unique Fetal Id.:	3
RIBS	(Skeletal) RIB 13, FULL - VARIATION; BILATERAL		
STERNUM	(Skeletal) STERNEBRA(E), MALALIGNED, SLIGHT TO MODERATE - VARIATION; 5, SLIGHT		
VERTEBRAL COLUMN	(Skeletal) VERTEBRAE, 27 PRESACRAL VERTEBRAE - VARIATION		
SKULL	(Skeletal) SKULL, ANOMALY - MALFORMATION; SQUAMOSALS MALFORMED HYOID, ANOMALY - MALFORMATION; ARCHES SMALL		
ABDOMEN	(Visceral) URETER(S), RETROCAVAL - VARIATION; RIGHT		

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UIC/TRL STUDY NO. 173 DEVELOPMENTAL TOXICITY STUDY OF WR6026 DIHYDROCHLORIDE IN RABBITS

INDIVIDUAL FETAL MORPHOLOGICAL OBSERVATIONS

GROUP 5: 300 MG/KG/DAY (RETINOL PALMITATE)

Animal: 789		Unique Fetal Id.: 2
Fetal Position: Left 02 *		
THORACIC CAVITY		
(Visceral)	HEART, HEART AND/OR GREAT VESSEL, ANOMALY - MALFORMATION;	
	AORTA--ENLARGED	
RIBS		
(Skeletal)	7TH CERVICAL RIB, PRESENT - VARIATION; LEFT	
STERNUM		
(Skeletal)	STERNEBRA(E), 5-6, UNOSSIFIED - VARIATION; 5 ONLY	
SKULL		
(Skeletal)	HYOID, ANOMALY - MALFORMATION; ARCHES ABSENT/UNOSSIFIED	
TAIL		
(External)	TAIL, ANOMALY - MALFORMATION; SHORT	
ABDOMEN		
(Visceral)	KIDNEY(S) AND/OR URETER(S), ANOMALY - MALFORMATION; RIGHT	
	KIDNEY, MISPLACED, MALFORMED, UNASCENDED	
HEAD		
(External)	HEAD, MICROCEPHALY - MALFORMATION	
	MOUTH, MACROSTOMIA - MALFORMATION	
	FACE, FACIAL BLEB(S) - MALFORMATION; BILATERAL	

Comments: SKELETAL CONFIRMATION OF EXTERNAL FINDINGS: SHORT TAIL--CAUDAL VERTEBRAE MALFORMED;
MICROCEPHALY--SKULL BONES MALFORMED

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UIC/TRL STUDY NO. 173 DEVELOPMENTAL TOXICITY STUDY OF WR6026 DIHYDROCHLORIDE IN RABBITS

INDIVIDUAL FETAL MORPHOLOGICAL OBSERVATIONS

GROUP 5: 300 MG/KG/DAY (RETINOL PALMITATE)

Animal: 791 (CONT.)

Fetal Position: Left 03 (CONT.) Unique Fetal Id.: 3

HEAD

(External) HEAD, FLESHY PROTUBERANCE - MALFORMATION
PINNA(E), PINNA(E) ANOMALY - MALFORMATION; BILATERAL, MALPOSITIONED AND SMALL IN SIZE
MOUTH, TONGUE/MANDIBLE ANOMALY - MALFORMATION; MANDIBLE MALFORMED
MOUTH, TONGUE, MACROGLOSSIA - MALFORMATION
FACE, FACIAL BLEB(S) - MALFORMATION; RIGHT

Comments: SKELETAL CONFIRMATION OF MALFORMED MANDIBLE

Fetal Position: Left 04 * Unique Fetal Id.: 4

RIBS

(Skeletal) RIB 13, FULL - VARIATION; BILATERAL

STERNUM

(Skeletal) STERNEBRA(E), MALALIGNED, SLIGHT TO MODERATE - VARIATION; 2-5

VERTEBRAL COLUMN

(Skeletal) VERTEBRAE, 27 PRESACRAL VERTEBRAE - VARIATION

SKULL

(Skeletal) SKULL, ANOMALY - MALFORMATION; SQUAMOSALS MALFORMED
HYOID, ANOMALY - MALFORMATION; ARCHES ABSENT/UNOSSIFIED

HEAD

(External) HEAD, FLESHY PROTUBERANCE - MALFORMATION; LEFT
PINNA(E), PINNA(E) ANOMALY - MALFORMATION; BILATERAL, SMALL
MOUTH, MACROSTOMIA - MALFORMATION
MOUTH, TONGUE/MANDIBLE ANOMALY - MALFORMATION; MANDIBLE MALFORMED
JAW, MAXILLAE, MICROGNATHIA - MALFORMATION
FACE, FACIAL BLEB(S) - MALFORMATION; RIGHT

Comments: SKELETAL CONFIRMATION OF MAXILLAE MICROGNATHIA AND MALFORMED MANDIBLE: SKULL BONES MALFORMED

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UIC/TRL STUDY NO. 173 DEVELOPMENTAL TOXICITY STUDY OF WR6026 DIHYDROCHLORIDE IN RABBITS

INDIVIDUAL FETAL MORPHOLOGICAL OBSERVATIONS

GROUP 5: 300 MG/KG/DAY (RETINOL PALMITATE)

Animal: 791 (CONT.)

Fetal Position: Left 05 *

THORACIC CAVITY

(Visceral) HEART, MAJOR BLOOD VESSEL, VARIATION - VARIATION; LEFT
CAROTID ARISES FROM THE BRACHIOCEPHALIC TRUNK

Unique Fetal Id.: 5

STERNUM

(Skeletal) STERNEBRA(E), MALALIGNED, SLIGHT TO MODERATE - VARIATION; 3, 4 AND 5, SLIGHT

SKULL

(Skeletal) SKULL, ANOMALY - MALFORMATION; JUGALS, SQUAMOSALS, PARIETALS MALFORMED
HYOID, ANOMALY - MALFORMATION; ARCHES MALPOSITIONED

ABDOMEN

(Visceral) URETER(S), RETROCAVAL - VARIATION; RIGHT

HEAD

(External) FACIAL PAPILLA(E), FACIAL PAPILLA(E) ANOMALY - MALFORMATION; BILATERAL, MALPOSITIONED
MOUTH, MACROSTOMIA - MALFORMATION
FACE, FACIAL BLEB(S) - MALFORMATION; LEFT

Fetal Position: Right 01

Unique Fetal Id.: 6

SKULL

(Skeletal) SKULL, ANOMALY - MALFORMATION; MAXILLAE, JUGALS, SQUAMOSALS MALFORMED
HYOID ARCH(ES), BENT - VARIATION; LEFT, MODERATE

HEAD

(External) MOUTH, MACROSTOMIA - MALFORMATION
MOUTH, TONGUE, MACROGLOSSIA - MALFORMATION
FACE, FACIAL BLEB(S) - MALFORMATION; BILATERAL

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UIC/TRL STUDY NO. 173 DEVELOPMENTAL TOXICITY STUDY OF WR6026 DIHYDROCHLORIDE IN RABBITS

INDIVIDUAL FETAL MORPHOLOGICAL OBSERVATIONS

GROUP 5: 300 MG/KG/DAY (RETINOL PALMITATE)

Animal:	793				Unique Fetal Id.: 2
Fetal Position:	Left 02 *				
ANUS					
(External)	ANUS, ANAL ATRESIA - MALFORMATION				
NECK					
(External)	NECK, FLESHY PROTUBERANCE - MALFORMATION				
THORACIC CAVITY					
(Visceral)	HEART, HEART AND/OR GREAT VESSEL, ANOMALY - MALFORMATION; COARCTATION OF THE AORTIC ARCH, INTERVENTRICULAR SEPTAL DEFECT HEART, MAJOR BLOOD VESSEL, VARIATION - VARIATION; RETROESOPHAGEAL RIGHT SUBCLAVIAN				
RIBS					
(Skeletal)	RIB 13, FULL - VARIATION; BILATERAL				
STERNUM					
(Skeletal)	STERNEBRA(E), MALALIGNED, SLIGHT TO MODERATE - VARIATION; 4 AND 5, SLIGHT				
VERTEBRAL COLUMN					
(Skeletal)	VERTEBRAE, ANOMALY - MALFORMATION; 7TH THORACIC CENTRUM, LOWER LUMBAR/UPPER SACRAL VERTEBRAE FUSED/MALFORMED				
SKULL					
(Skeletal)	SKULL, ANOMALY - MALFORMATION; JUGALS, SQUAMOSALS MALFORMED				
TAIL					
(External)	TAIL, ANOMALY - MALFORMATION; SHORT				
ABDOMEN					
(Visceral)	GALL BLADDER, VARIATION - VARIATION; SMALL KIDNEY(S) AND/OR URETER(S), ANOMALY - MALFORMATION; RIGHT URETER ABSENT; LEFT KIDNEY MISSHAPEN; LEFT URETER SMALL; RIGHT KIDNEY ABSENT				

Comments: SKELETAL CONFIRMATION OF SHORT TAIL: CAUDAL VERTEBRAE ABSENT/FUSED/MALFORMED

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UIC/TRL STUDY NO. 173 DEVELOPMENTAL TOXICITY STUDY OF WR6026 DIHYDROCHLORIDE IN RABBITS

INDIVIDUAL FETAL MORPHOLOGICAL OBSERVATIONS

GROUP 5: 300 MG/KG/DAY (RETINOL PALMITATE)

Animal: 793 (CONT.)	Unique Fetal Id.: 4
Fetal Position: Left 04	
ANUS	(External) ANAL OPENING, SMALL IN SIZE - MALFORMATION; UNOPENED
THORACIC CAVITY	
(Visceral)	HEART, MAJOR BLOOD VESSEL, VARIATION - VARIATION; ACCESSORY LEFT SUBCLAVIAN, RIGHT CAROTID ARISES FROM THE BRACHIOCEPHALIC TRUNK
RIBS	
(Skeletal)	RIB 13, FULL - VARIATION; BILATERAL
STERNUM	
(Skeletal)	STERNEBRA(E), MALALIGNED, SLIGHT TO MODERATE - VARIATION; 4 AND 5
VERTEBRAL COLUMN	
(Skeletal)	VERTEBRAE, 27 PRESACRAL VERTEBRAE - VARIATION
SKULL	
(Skeletal)	SKULL, ANOMALY - MALFORMATION; MAXILLAE, JUGALS, SQUAMOSALS, PARIETALS MALFORMED HYOID, ANOMALY - MALFORMATION; ARCHES ABSENT/UNOSSIFIED
ABDOMEN	
(External)	GENITAL TUBULE, SMALL IN SIZE - MALFORMATION
HEAD	
(External)	PINNA(E), PINNA(E) ANOMALY - MALFORMATION; SMALL IN SIZE MOUTH, MACROSTOMIA - MALFORMATION FACE, FACIAL BLEB(S) - MALFORMATION

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UIC/TRL STUDY NO. 173 DEVELOPMENTAL TOXICITY STUDY OF WR6026 DIHYDROCHLORIDE IN RABBITS

INDIVIDUAL FETAL MORPHOLOGICAL OBSERVATIONS

GROUP 5: 300 MG/KG/DAY (RETINOL PALMITATE)

Animal: 793 (CONT.)

Fetal Position: Left 06 * Unique Fetal Id.: 6

(Skeletal) RIB 13, FULL - VARIATION; BILATERAL

VERTEBRAL COLUMN

(Skeletal) VERTEBRAE, ANOMALY - MALFORMATION; SACRAL VERTEBRAE FUSED/MALFORMED

SKULL

(Skeletal) SKULL, ANOMALY - MALFORMATION; MAXILLAE, JUGALS, SQUAMOSALS, PARIETALS MALFORMED
HYOID, ANOMALY - MALFORMATION; RIGHT ARCH SMALL
PALATE, CLEFT PALATE - MALFORMATION

TAIL

(External) TAIL, ANOMALY - MALFORMATION; ABSENT

HEAD

(External) MOUTH, MACROSTOMIA - MALFORMATION
FACE, FACIAL BLEB(S) - MALFORMATION

Comments: SKELETAL CONFIRMATION OF ABSENT TAIL: MAJORITY OF CAUDAL VERTEBRAE ABSENT

Fetal Position: Left 07
RIBS

Unique Fetal Id.: 7

(Skeletal) RIB 13, FULL - VARIATION; BILATERAL

STERNUM

(Skeletal) STERNEBRA(E), 5-6, UNOSSIFIED - VARIATION

VERTEBRAL COLUMN

(Skeletal) VERTEBRAE, 27 PRESACRAL VERTEBRAE - VARIATION

SKULL

(Skeletal) SKULL, ANOMALY - MALFORMATION; LEFT SQUAMOSAL MALFORMED

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UIC/TRL STUDY NO. 173 DEVELOPMENTAL TOXICITY STUDY OF WR6026 DIHYDROCHLORIDE IN RABBITS

INDIVIDUAL FETAL MORPHOLOGICAL OBSERVATIONS

GROUP 5: 300 MG/KG/DAY (RETINOL PALMITATE)

Animal: 793 (CONT.)	Unique Fetal Id.: 8
Fetal Position: Left 08	
NECK	(External) NECK, FLESHY PROTUBERANCE - MALFORMATION
RIBS	(Skeletal) RIB 13, FULL - VARIATION; BILATERAL
STERNUM	(Skeletal) STERNEBRA(E), MALALIGNED, SLIGHT TO MODERATE - VARIATION; 2-5
VERTEBRAL COLUMN	(Skeletal) VERTEBRAE, 27 PRESACRAL VERTEBRAE - VARIATION
SKULL	(Skeletal) SKULL, ANOMALY - MALFORMATION; LEFT SQUAMOSAL MALFORMED
ABDOMEN	(Visceral) KIDNEY(S) AND/OR URETER(S), ANOMALY - MALFORMATION; LEFT KIDNEY AND URETER ABSENT
Fetal Position: Right 01	Unique Fetal Id.: 9
NECK	(External) NECK, FLESHY PROTUBERANCE - MALFORMATION
RIBS	(Skeletal) RIB 13, FULL - VARIATION; LEFT FULL, RIGHT RUDIMENTARY
STERNUM	(Skeletal) STERNEBRA(E), MALALIGNED, SLIGHT TO MODERATE - VARIATION; 3 AND 4, SLIGHT
SKULL	(Skeletal) SKULL, ANOMALY - MALFORMATION; MAXILLAE, JUGALS, SQUAMOSALS, PARIETALS MALFORMED HYOID, ANOMALY - MALFORMATION; LEFT ARCH ABSENT/UNOSSIFIED PALATE, CLEFT PALATE - MALFORMATION
ABDOMEN	(Visceral) KIDNEY(S) AND/OR URETER(S), ANOMALY - MALFORMATION; LEFT KIDNEY SMALL AND UNASCENDED
HEAD	(External) MOUTH, MACROSTOMIA - MALFORMATION FACE, FACIAL BLEB(S) - MALFORMATION

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UIC/TRL STUDY NO. 173 / DEVELOPMENTAL TOXICITY STUDY OF WR6026 DIHYDROCHLORIDE IN RABBITS
INDIVIDUAL FETAL MORPHOLOGICAL OBSERVATIONS

GROUP 5: 300 MG/KG/DAY (RETINOL PALMITATE)

Animal: 794		Unique Fetal Id.: 1
Fetal Position: Left 01 *		
ANUS	(External) ANUS, ANAL ATRESIA - MALFORMATION	
SKULL	(Skeletal) SKULL, ANOMALY - MALFORMATION; MAXILLAE, JUGALS, SQUAMOSALS MALFORMED HYOID, ANOMALY - MALFORMATION; RIGHT ARCH ABSENT/UNOSSIFIED	
TAIL	(External) TAIL, ANOMALY - MALFORMATION; SHORT	
HEAD	(External) PINNA(E), PINNA(E) ANOMALY - MALFORMATION; BILATERAL, SMALL IN SIZE MOUTH, MACROSTOMIA - MALFORMATION FACE, FACIAL BLEB(S) - MALFORMATION	
Comments: SKELETAL CONFIRMATION OF SHORT TAIL: CAUDAL VERTEBRAE ABSENT/FUSED		
Fetal Position: Left 02		Unique Fetal Id.: 2
SKULL	(Skeletal) SKULL, ANOMALY - MALFORMATION; LEFT SQUAMOSAL MALFORMED	
Fetal Position: Left 03 *		Unique Fetal Id.: 3
SKULL	(Skeletal) SKULL, ANOMALY - MALFORMATION; MAXILLAE, JUGALS, SQUAMOSALS, SUPRAOCCIPITAL MALFORMED	
TAIL	(External) TAIL, ANOMALY - MALFORMATION; BENT	
ABDOMEN	(Visceral) KIDNEY(S) AND/OR URETER(S), ANOMALY - MALFORMATION; LEFT KIDNEY AND URETER ABSENT	
HEAD	(External) MOUTH, MACROSTOMIA - MALFORMATION FACE, FACIAL BLEB(S) - MALFORMATION	
Comments: SKELETAL CONFIRMATION OF BENT TAIL: CAUDAL VERTEBRA MALPOSITIONED		

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UIC/TRL STUDY NO. 173 DEVELOPMENTAL TOXICITY STUDY OF WR6026 DIHYDROCHLORIDE IN RABBITS
INDIVIDUAL FETAL MORPHOLOGICAL OBSERVATIONS

GROUP 5: 300 MG/KG/DAY (RETINOL PALMITATE)

Animal: 794 (CONT.)	Unique Fetal Id.: 4
Fetal Position: Right 01	
RIBS	(Skeletal) RIB 13, FULL - VARIATION; BILATERAL
SKULL	(Skeletal) SKULL, ANOMALY - MALFORMATION; MAXILLAE, JUGALS, SQUAMOSALS MALFORMED HYOID, ANOMALY - MALFORMATION; LEFT ARCH ABSENT/UNOSSIFIED, BODY MALFORMED
HEAD	(External) PINNA(E), PINNA(E) ANOMALY - MALFORMATION; BILATERAL, SMALL IN SIZE
Fetal Position: Right 02	Unique Fetal Id.: 5
SKULL	(Skeletal) SKULL, ANOMALY - MALFORMATION; MAXILLAE, JUGALS, SQUAMOSALS MALFORMED
HEAD	(External) FACE, FACIAL BLEB(S) - MALFORMATION
Fetal Position: Right 03 *	Unique Fetal Id.: 6
RIBS	(Skeletal) RIB 13, FULL - VARIATION; LEFT FULL, RIGHT RUDIMENTARY
VERTEBRAL COLUMN	(Skeletal) VERTEBRAE, 27 PRESACRAL VERTEBRAE - VARIATION
SKULL	(Skeletal) SKULL, ANOMALY - MALFORMATION; SQUAMOSALS MALFORMED
TAIL	(External) TAIL, ANOMALY - MALFORMATION; BENT
HEAD	(External) PINNA(E), PINNA(E) ANOMALY - MALFORMATION; BILATERAL, MALPOSITIONED AND SMALL IN SIZE

Comments: SKELETAL CONFIRMATION OF BENT TAIL: CAUDAL VERTEBRAE MALPOSITIONED

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UIC/TRL STUDY NO. 173 DEVELOPMENTAL TOXICITY STUDY OF WR6026 DIHYDROCHLORIDE IN RABBITS

INDIVIDUAL FETAL MORPHOLOGICAL OBSERVATIONS

GROUP 5: 300 MG/KG/DAY (RETINOL PALMITATE)

Animal: 794 (CONT.)

Fetal Position: Right 04
VERTEBRAL COLUMN

Unique Fetal Id.: 7

(Skeletal) VERTEBRAE, 27 PRESACRAL VERTEBRAE - VARIATION
CAUDAL VERTEBRAE, ANOMALY - MALFORMATION; DISTAL--FUSED/MALFORMED

SKULL

(Skeletal) SKULL, ANOMALY - MALFORMATION; LEFT SQUAMOSAL FUSED TO LEFT PARIETAL
HYOID ARCH(ES), BENT - VARIATION; RIGHT, SLIGHT

Fetal Position: Right 05 *

Unique Fetal Id.: 8

SKULL

(Skeletal) SKULL, ANOMALY - MALFORMATION; MAXILLAE, JUGALS, SQUAMOSALS, SUPRAOCCIPITAL MALFORMED

TAIL

(External) TAIL, ANOMALY - MALFORMATION; ABSENT

HEAD

(External) MOUTH, MACROSTOMIA - MALFORMATION
FACE, FACIAL BLEB(S) - MALFORMATION

Comments: SKELETAL CONFIRMATION OF ABSENT TAIL: ALMOST ALL CAUDAL VERTEBRAE ABSENT

Fetal Position: Right 06

Unique Fetal Id.: 9

SKULL

(Skeletal) HYOID, ANOMALY - MALFORMATION; ARCHES ABSENT/UNOSSIFIED

ABDOMEN

(Visceral) KIDNEY(S) AND/OR URETER(S), ANOMALY - MALFORMATION; RIGHT KIDNEY AND URETER ABSENT

APPENDIX D

UIC/TRL STUDY NO. 173 DEVELOPMENTAL TOXICITY STUDY OF WR6026 DIHYDROCHLORIDE IN RABBITS

INDIVIDUAL FETAL MORPHOLOGICAL OBSERVATIONS

GROUP 5: 300 MG/KG/DAY (RETINOL PALMITATE)

Animal: 795	Unique Fetal Id.: 2
Fetal Position: Left 02	
STERNUM	
(Skeletal) STERNEBRA(E), MALALIGNED, SLIGHT TO MODERATE - VARIATION; 4, 5 AND 6, SLIGHT	
VERTEBRAL COLUMN	
(Skeletal) VERTEBRAE, 27 PRESACRAL VERTEBRAE - VARIATION	
SKULL	
(Skeletal) SKULL, ANOMALY - MALFORMATION; SQUAMOSALS MALFORMED	
HEAD	
(External) PINNA(E), PINNA(E) ANOMALY - MALFORMATION; BILATERAL, MALPOSITIONED; SMALL	
Fetal Position: Left 03	Unique Fetal Id.: 3
THORACIC CAVITY	
(Visceral) HEART, MAJOR BLOOD VESSEL, VARIATION - VARIATION; LEFT	
CAROTID ARISES FROM BRACHIOCEPHALIC TRUNK	
RIBS	
(Skeletal) RIB 13, FULL - VARIATION; BILATERAL	
VERTEBRAL COLUMN	
(Skeletal) VERTEBRAE, 27 PRESACRAL VERTEBRAE - VARIATION	
SKULL	
(Skeletal) SKULL, ANOMALY - MALFORMATION; SQUAMOSALS, PARIETALS MALFORMED	
HYOID, ANOMALY - MALFORMATION; ARCHES ABSENT/UNOSSIFIED, BODY MALFORMED	
HEAD	
(External) PINNA(E), PINNA(E) ANOMALY - MALFORMATION; BILATERAL, MALPOSITIONED; SMALL	

APPENDIX D

UIC/TRL STUDY NO. 173 DEVELOPMENTAL TOXICITY STUDY OF WR6026 DIHYDROCHLORIDE IN RABBITS

INDIVIDUAL FETAL MORPHOLOGICAL OBSERVATIONS

GROUP 5: 300 MG/KG/DAY (RETINOL PALMITATE)

Animal: 795 (CONT.)	Unique Fetal Id.: 6
Fetal Position: Right 03	
RIBS	(Skeletal) RIB 13, FULL - VARIATION; LEFT RUDIMENTARY, RIGHT FULL
VERTEBRAL COLUMN	(Skeletal) VERTEBRAE, 27 PRESACRAL VERTEBRAE - VARIATION
SKULL	(Skeletal) SKULL, ANOMALY - MALFORMATION; RIGHT SQUAMOSAL MALFORMED HYOID, ANOMALY - MALFORMATION; LEFT ARCH ABSENT/UNOSSIFIED, RIGHT ARCH SMALL, BODY MALFORMED
HEAD	(External) PINNA(E), PINNA(E) ANOMALY - MALFORMATION; BILATERAL, MALPOSITIONED; SMALL
Fetal Position: Right 04	Unique Fetal Id.: 7
RIBS	(Skeletal) RIB 13, FULL - VARIATION; RIGHT
VERTEBRAL COLUMN	(Skeletal) VERTEBRAE, 27 PRESACRAL VERTEBRAE - VARIATION
SKULL	(Skeletal) SKULL, ANOMALY - MALFORMATION; SQUAMOSALS MALFORMED HYOID, ANOMALY - MALFORMATION; ARCHES SMALL, BODY MALFORMED
HEAD	(External) PINNA(E), PINNA(E) ANOMALY - MALFORMATION; BILATERAL, MALPOSITIONED; SMALL
Fetal Position: Right 05	Unique Fetal Id.: 8
RIBS	(Skeletal) RIB 13, FULL - VARIATION; BILATERAL
VERTEBRAL COLUMN	(Skeletal) VERTEBRAE, 27 PRESACRAL VERTEBRAE - VARIATION
SKULL	(Skeletal) HYOID, ANOMALY - MALFORMATION; ARCHES ABSENT/UNOSSIFIED
ABDOMEN	(Visceral) GALL BLADDER, VARIATION - VARIATION; SMALL

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APPENDIX D

UIC/TRL STUDY NO. 173 DEVELOPMENTAL TOXICITY STUDY OF WR6026 DIHYDROCHLORIDE IN RABBITS

INDIVIDUAL FETAL MORPHOLOGICAL OBSERVATIONS

GROUP 5: 300 MG/KG/DAY (RETINOL PALMITATE)

Animal: 795 (CONT.)	Unique Fetal Id.: 9
Fetal Position: Right 06	
THORACIC CAVITY	
(Visceral)	HEART, MAJOR BLOOD VESSEL, VARIATION - VARIATION; LEFT CAROTID ARISES FROM BRACHIOCEPHALIC TRUNK
RIBS	
(Skeletal)	RIB 13, RUDIMENTARY - VARIATION; BILATERAL (LEFT--NO ARTICULATING HEAD)
VERTEBRAL COLUMN	
(Skeletal)	VERTEBRAE, 27 PRESACRAL VERTEBRAE - VARIATION CAUDAL VERTEBRAE, ANOMALY - MALFORMATION; CAUDAL VERTEBRA MALPOSITIONED
SKULL	
(Skeletal)	SKULL, ANOMALY - MALFORMATION; SQUAMOSALS MALFORMED HYOID, ANOMALY - MALFORMATION; ARCHES ABSENT/UNOSSIFIED
HEAD	
(External)	PINNA(E), PINNA(E) ANOMALY - MALFORMATION; MALPOSITIONED AND SMALL
Animal: 796	Unique Fetal Id.: 2
Fetal Position: Left 02	
THORACIC CAVITY	
(Visceral)	HEART, HEART AND/OR GREAT VESSEL, ANOMALY - MALFORMATION; COMMON TRUNCUS ARTERIOSIS, INTERVENTRICULAR SEPTAL DEFECT
STERNUM	
(Skeletal)	STERNEBRA(E), MALALIGNED, SLIGHT TO MODERATE - VARIATION; 5, SLIGHT
SKULL	
(Skeletal)	SKULL, ANOMALY - MALFORMATION; SQUAMOSALS MALFORMED PALATE, CLEFT PALATE - MALFORMATION HYOID ARCH(ES), BENT - VARIATION; RIGHT, MODERATE
HINDLIMBS	
(Skeletal)	CALCANEUS, UNOSSIFIED - VARIATION; BILATERAL

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UIC/TRL STUDY NO. 173 DEVELOPMENTAL TOXICITY STUDY OF WR6026 DIHYDROCHLORIDE IN RABBITS

INDIVIDUAL FETAL MORPHOLOGICAL OBSERVATIONS

GROUP 5: 300 MG/KG/DAY (RETINOL PALMITATE)

Animal: 797	Unique Fetal Id.: 3
Fetal Position: Left 03	
RIBS	(Skeletal) RIB 13, FULL - VARIATION; BILATERAL
VERTEBRAL COLUMN	(Skeletal) VERTEBRAE, 27 PRESACRAL VERTEBRAE - VARIATION
SKULL	(Skeletal) SKULL, ANOMALY - MALFORMATION; SQUAMOSALS MALFORMED, INTERPARIETAL ABSENT/UNOSSIFIED HYOID, ANOMALY - MALFORMATION; BODY MALFORMED, LEFT ARCH ABSENT/UNOSSIFIED, RIGHT ARCH SMALL
Fetal Position: Right 01	Unique Fetal Id.: 4
RIBS	(Skeletal) RIB 13, FULL - VARIATION; BILATERAL
SKULL	(Skeletal) SKULL, ANOMALY - MALFORMATION; SQUAMOSALS MALFORMED, INTERPARIETAL SMALL HYOID, ANOMALY - MALFORMATION; ARCHES ABSENT/UNOSSIFIED, BODY MALFORMED
HEAD	(External) PINNA(E), PINNA(E) ANOMALY - MALFORMATION; SMALL IN SIZE
Fetal Position: Right 03	Unique Fetal Id.: 6
RIBS	(Skeletal) RIB 13, FULL - VARIATION; BILATERAL
STERNUM	(Skeletal) STERNEBRA(E), MALALIGNED, SLIGHT TO MODERATE - VARIATION; 3, SLIGHT
VERTEBRAL COLUMN	(Skeletal) VERTEBRAE, 27 PRESACRAL VERTEBRAE - VARIATION
SKULL	(Skeletal) SKULL, ANOMALY - MALFORMATION; SQUAMOSALS MALFORMED, INTERPARIETAL ABSENT/UNOSSIFIED

APPENDIX D

UIC/TRL STUDY NO. 173 DEVELOPMENTAL TOXICITY STUDY OF WR6026 DIHYDROCHLORIDE IN RABBITS

INDIVIDUAL FETAL MORPHOLOGICAL OBSERVATIONS

GROUP 5: 300 MG/KG/DAY (RETINOL PALMITATE)

Animal: 797 (CONT.)	Unique Fetal Id.: 7
Fetal Position: Right 04	
THORACIC CAVITY	
(Visceral) HEART, MAJOR BLOOD VESSEL, VARIATION - VARIATION; LEFT	
CAROTID ARISES FROM THE BRACHIOCEPHALIC TRUNK	
RIBS	
(Skeletal) RIB 13, FULL - VARIATION; BILATERAL	
VERTEBRAL COLUMN	
(Skeletal) VERTEBRAE, 27 PRESACRAL VERTEBRAE - VARIATION	
SKULL	
(Skeletal) SKULL, ANOMALY - MALFORMATION; SQUAMOSALS MALFORMED, INTERPARIETAL ABSENT/UNOSSIFIED	
Fetal Position: Right 05	Unique Fetal Id.: 8
RIBS	
(Skeletal) RIB 13, FULL - VARIATION; BILATERAL	
VERTEBRAL COLUMN	
(Skeletal) VERTEBRAE, 27 PRESACRAL VERTEBRAE - VARIATION	
SKULL	
(Skeletal) SKULL, ANOMALY - MALFORMATION; SQUAMOSALS MALFORMED, INTERPARIETAL ABSENT/UNOSSIFIED	
HYOID, ANOMALY - MALFORMATION; LEFT ARCH SMALL, RIGHT ARCH ABSENT/UNOSSIFIED	
HEAD	
(External) PINNA(E), PINNA(E) ANOMALY - MALFORMATION; SMALL IN SIZE	
Animal: 798	Unique Fetal Id.: 2
Fetal Position: Left 02	
STERNUM	
(Skeletal) STERNEBRA(E), MALALIGNED AND FUSED - MALFORMATION; 4 AND 5 FUSED; 2, 3 AND 4 MALALIGNED SLIGHT	
SKULL	
(Skeletal) HYOID, ANOMALY - MALFORMATION; LEFT ARCH ABSENT/UNOSSIFIED, RIGHT ARCH SMALL	

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UIC/TRL STUDY NO. 173 DEVELOPMENTAL TOXICITY STUDY OF WR6026 DIHYDROCHLORIDE IN RABBITS

INDIVIDUAL FETAL MORPHOLOGICAL OBSERVATIONS

GROUP 5: 300 MG/KG/DAY (RETINOL PALMITATE)

Animal: 798 (CONT.)

Fetal Position: Left 03
THORACIC CAVITY

Unique Fetal Id.: 3

(Visceral) HEART, MAJOR BLOOD VESSEL, VARIATION - VARIATION; LEFT
CAROTID ARISES FROM THE BRACHIOCEPHALIC TRUNK

RIBS

(Skeletal) RIB 13, FULL - VARIATION; BILATERAL (NO ARTICULATING HEADS)

STERNUM

(Skeletal) STERNEBRA (E), 5-6, UNOSSIFIED - VARIATION; 6 ONLY

SKULL

(Skeletal) HYOID ARCH(ES), BENT - VARIATION; LEFT, MODERATE

Fetal Position: Left 04
STERNUM

Unique Fetal Id.: 4

(Skeletal) STERNEBRA (E), MALALIGNED, SLIGHT TO MODERATE - VARIATION; 5 AND 6, SLIGHT

SKULL

(Skeletal) HYOID ARCH(ES), BENT - VARIATION; RIGHT, MODERATE

Fetal Position: Left 05
STERNUM

Unique Fetal Id.: 5

(Skeletal) STERNEBRA (E), MALALIGNED AND FUSED - MALFORMATION; 4 AND 5 FUSED; 2-5 MALALIGNED SLIGHT TO MODERATE

Fetal Position: Right 01
SKULL

Unique Fetal Id.: 6

(Skeletal) HYOID, ANOMALY - MALFORMATION; LEFT ARCH ABSENT/UNOSSIFIED

Fetal Position: Right 04
STERNUM

Unique Fetal Id.: 9

(Skeletal) STERNEBRA (E), MALALIGNED, SLIGHT TO MODERATE - VARIATION; 2 AND 3, SLIGHT

APPENDIX D

UIC/TRL STUDY NO. 173 DEVELOPMENTAL TOXICITY STUDY OF WR6026 DIHYDROCHLORIDE IN RABBITS
INDIVIDUAL FETAL MORPHOLOGICAL OBSERVATIONS

GROUP 5: 300 MG/KG/DAY (RETINOL PALMITATE)

Animal: 800		Unique Fetal Id.: 1
Fetal Position: Left 01		
SKULL		
(Skeletal)	SKULL, ANOMALY - MALFORMATION; SQUAMOSALS MALFORMED	
	HYOID, ANOMALY - MALFORMATION; ARCHES ABSENT/UNOSSIFIED	
ABDOMEN		
(Visceral)	URETER(S), RETROCAVAL - VARIATION; RIGHT	
	GALL BLADDER, VARIATION - VARIATION; ABSENT	
Fetal Position: Left 02		Unique Fetal Id.: 2
THORACIC CAVITY		
(Visceral)	HEART, MAJOR BLOOD VESSEL, VARIATION - VARIATION; LEFT	
	CAROTID ARISES FROM THE BRACHIOCEPHALIC TRUNK	
RIBS		
(Skeletal)	RIB 13, FULL - VARIATION; BILATERAL	
STERNUM		
(Skeletal)	STERNEBRA(E), 5-6, UNOSSIFIED - VARIATION; 6 ONLY	
VERTEBRAL COLUMN		
(Skeletal)	VERTEBRAE, 27 PRESACRAL VERTEBRAE - VARIATION	
SKULL		
(Skeletal)	SKULL, ANOMALY - MALFORMATION; SQUAMOSALS MALFORMED	
	HYOID, ANOMALY - MALFORMATION; ARCHES ABSENT/UNOSSIFIED	
ABDOMEN		
(Visceral)	GALL BLADDER, VARIATION - VARIATION; SMALL	
HEAD		
(External)	PINNA(E), PINNA(E) ANOMALY - MALFORMATION; BILATERAL, MALPOSITIONED; SMALL IN SIZE	

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UIC/TRL STUDY NO. 173 DEVELOPMENTAL TOXICITY STUDY OF WR6026 DIHYDROCHLORIDE IN RABBITS

INDIVIDUAL FETAL MORPHOLOGICAL OBSERVATIONS

GROUP 5: 300 MG/KG/DAY (RETINOL PALMITATE)

Animal: 800 (CONT.)	Unique Fetal Id.: 3
Fetal Position: Left 03	
RIBS	
(Skeletal) RIB 13, RUDIMENTARY - VARIATION; RIGHT (NO ARTICULATING HEAD)	
STERNUM	
(Skeletal) STERNEBRA(E), MALALIGNED, SLIGHT TO MODERATE - VARIATION; 3 AND 4, SLIGHT	
SKULL	
(Skeletal) SKULL, ANOMALY - MALFORMATION; MAXILLAE, SQUAMOSALS, SUPRAOCCIPITAL MALFORMED	
HYOID, ANOMALY - MALFORMATION; ARCHES ABSENT/UNOSSIFIED	
HINDLIMBS	
(Skeletal) TALUS, UNOSSIFIED - VARIATION; BILATERAL	
Fetal Position: Left 04	Unique Fetal Id.: 4
STERNUM	
(Skeletal) STERNEBRA(E), 5-6, UNOSSIFIED - VARIATION; 5 ONLY	
SKULL	
(Skeletal) SKULL, ANOMALY - MALFORMATION; MAXILLAE, SQUAMOSALS MALFORMED	
HYOID, ANOMALY - MALFORMATION; ARCHES SMALL, BODY MALFORMED	
Fetal Position: Right 01	Unique Fetal Id.: 5
RIBS	
(Skeletal) RIB 13, RUDIMENTARY - VARIATION; RIGHT (NO ARTICULATING HEAD)	
7TH CERVICAL RIB, PRESENT - VARIATION; RIGHT	
STERNUM	
(Skeletal) STERNEBRA(E), MALALIGNED, SLIGHT TO MODERATE - VARIATION; 5, SLIGHT	
VERTEBRAL COLUMN	
(Skeletal) CAUDAL VERTEBRAE, ANOMALY - MALFORMATION; 2 FUSED	
SKULL	
(Skeletal) SKULL, ANOMALY - MALFORMATION; MAXILLAE MALFORMED	
HYOID, ANOMALY - MALFORMATION; ARCHES ABSENT/UNOSSIFIED, BODY MALFORMED	

APPENDIX D

UIC/TRL STUDY NO. 173 DEVELOPMENTAL TOXICITY STUDY OF WR6026 DIHYDROCHLORIDE IN RABBITS

INDIVIDUAL FETAL MORPHOLOGICAL OBSERVATIONS

GROUP 5: 300 MG/KG/DAY (RETINOL PALMITATE)

Animal: 800 (CONT.)
 Fetal Position: Right 02 * Unique Fetal Id.: 6

ANUS (External) ANUS, ANAL ATRESIA - MALFORMATION

RIBS (Skeletal) 7TH CERVICAL RIB, PRESENT - VARIATION; BILATERAL

STERNUM (Skeletal) STERNEBRA(E), 5-6, UNOSSIFIED - VARIATION; 5 ONLY

VERTEBRAL COLUMN (Skeletal) VERTEBRAE, 27 PRESACRAL VERTEBRAE - VARIATION

SKULL (Skeletal) SKULL, ANOMALY - MALFORMATION; MAXILLAE, SQUAMOSALS MALFORMED
 HYOID, ANOMALY - MALFORMATION; ARCHES ABSENT/UNOSSIFIED, BODY MALFORMED

TAIL (External) TAIL, ANOMALY - MALFORMATION; ABSENT

ABDOMEN (Visceral) GALL BLADDER, VARIATION - VARIATION; SMALL

HEAD (External) PINNA(E), PINNA(E) ANOMALY - MALFORMATION; BILATERAL, MALPOSITIONED; SMALL IN SIZE

Comments: SKELETAL CONFIRMATION OF ABSENT TAIL: ALMOST ALL CAUDAL VERTEBRAE ABSENT, SACRAL VERTEBRA 4 MALFORMED

Fetal Position: Right 03 Unique Fetal Id.: 7

SKULL (Skeletal) SKULL, ANOMALY - MALFORMATION; MAXILLAE, SQUAMOSALS MALFORMED
 HYOID, ANOMALY - MALFORMATION; ARCHES ABSENT/UNOSSIFIED

HEAD (External) FACE, FACIAL BLEB(S) - MALFORMATION

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UIC/TRL STUDY NO. 173 DEVELOPMENTAL TOXICITY STUDY OF WR6026 DIHYDROCHLORIDE IN RABBITS

INDIVIDUAL FETAL MORPHOLOGICAL OBSERVATIONS

GROUP 5: 300 MG/KG/DAY (RETINOL PALMITATE)

Animal: 800 (CONT.)	Unique Fetal Id.: 9
Fetal Position: Right 05	
SKULL	
(Skeletal) SKULL, ANOMALY - MALFORMATION; MAXILLAE, SQUAMOSALS MALFORMED	
HYOID, ANOMALY - MALFORMATION; ARCHES SMALL	
ABDOMEN	
(Visceral) KIDNEY(S) AND/OR URETER(S), ANOMALY - MALFORMATION; LEFT KIDNEY ABSENT	

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APPENDIX 6

Protocol and Amendments

DEVELOPMENTAL TOXICITY (SEGMENT II)
STUDY OF WR6026 DIHYDROCHLORIDE IN RABBITS

DRAFT

1.0 PURPOSE OF THE STUDY:

The purpose of this study is to evaluate the embryo/fetal toxicity and the teratogenic potential of WR6026 Dihydrochloride in rabbits. The protocol conforms to the standards of the U.S. Food and Drug Administration, the requirements of the Committee on Safety of Medicines in Great Britain, and the Organization for Economic Cooperation and Development. The protocol for this study was approved by the UIC Animal Care Committee (Appendix 1).

2.0 SPONSOR:

- 2.1 Name: U.S. Army Medical Materiel
Development Activity
- 2.2 Address: Fort Detrick
Frederick, MD 21702-5009
- 2.3 Representative: George J. Schieferstein, Ph.D.

3.0 TESTING FACILITY:

- 3.1 Name: Toxicology Research Laboratory (TRL)
- 3.2 Address: University of Illinois at Chicago (UIC)
Department of Pharmacology
1940 W. Taylor St.
Chicago, Illinois 60612 - 7353
- 3.3 Study Director: Barry S. Levine, D.Sc., D.A.B.T.

4.0 DATES:

- 4.1 Proposed Initiation of In-Life Phase: 03/07/95
- 4.2 Proposed Completion of In-Life Phase: 04/07/95
- 4.3 Proposed Study Completion Date
(Draft Final Report): 07/07/95

REVISED PAGE	
STUDY NO: 173	INITIAL: BSL
DATE: 3/27/95	

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5.0 TEST ARTICLE

- 5.1 Name or Code No: WR6026 Dihydrochloride (base mole fraction = 0.825)
6-Methoxy-8-(6-diethylaminohexylamino) lepidine
dihydrochloride
Bottle number BK01845
- 5.2 TRL Chemical No: 1540614
- 5.3 Physical Description: Light yellow powder
- 5.4 Storage Conditions to Maintain Stability:
- 5.4.1 Temperature: -16° to -20° during storage. 0° to 4°C following dosage form preparation.
- 5.4.2 Humidity: Hygroscopic, keep tightly closed in a desiccator.
- 5.4.3 Light: Protect from light; amber bottle or silver foil covering.
- 5.4.4 Special Requirements: None.
- 5.5 Special Handling Procedures: Standard safety precautions will be followed including gloves, eye protection, mask, and lab coats.
- 5.6 Log of Test Article: The amount, date, identity of person(s) removing aliquots and the purpose for which each aliquot of the test article was removed from the batch will be documented. At termination of the study, all unused test article will be returned to the Sponsor.

6.0 PERSONNEL:

Study Director	Barry S. Levine, D.Sc., D.A.B.T.
Reproductive Toxicologist	Ashraf F. Youssef, M.D., Ph.D.
Reproductive Scientist	Roberto A. Matamoros, D.V.M., Ph.D.
Teratologist (PAI)	Michael D. Mercieca, B.S.
Analytical Chemist	Adam Negrusz, Ph.D.
Clinical Veterinarian	James Artwohl, D.V.M., M.S., D.A.C.L.A.M.
Veterinarian Support	Documented in raw data
Tox. Lab Supervisor	Soudabeh Soura, B.S.
Lead Technician	Nancy Dinger, B.S.
Chemistry Specialist	Thomas Tolhurst, B.S.
Quality Assurance	Ronald C. Schoenbeck

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7.0 TEST SYSTEM:

- 7.1 Species: Rabbit
- 7.2 Strain: New Zealand White (Pasteurella Free)
- 7.3 Sex(s)/Number: 100 time-mated females (day 0 = day of observed mating)
- 7.4 Weight of Animals: ≈3.0 - 4.0 kg at start of study
- 7.5 Age of Animals: ≈5 to 6 months at study initiation.
- 7.6 Source of Animals: HRP, Inc., Denver, PA.
- 7.7 Justification for Selection of Test System: The FDA requires the use of two animal species, one being a non-rodent, in preclinical developmental toxicity studies. The rabbit is a standard and accepted non-rodent species for regulatory developmental toxicology studies, and is specified by the Sponsor. In addition, the New Zealand white rabbit was selected because it has demonstrated sensitivity to developmental toxicants and historical data and experience exist.
- 7.8 Procedure for Unique Identification of Test System: Each animal will be given a facility-unique number (ear tag) by the Supplier, and a separate study-unique number (ear tag) upon arrival at UIC. This latter number will also appear on a cage card visible on the front of each cage. The cage card will additionally contain the study number, test or control article identification, dose level, and treatment group. Raw data records and specimens will also be identified by the unique animal number.
- 7.9 Housing: The animals will be housed in an AAALAC-accredited facility. Animals will be singly housed in stainless steel cages in a temperature (61-69°F) and humidity (30 - 70%) controlled room with a 14 hour light/10 hour dark cycle. The cage size, 0.32 m² area and 38.0 cm height, is adequate to house rabbits for this study as described in the *Guide for the Care and Use of Laboratory Animals*, DHHS (NIH) No. 86.23.
- 7.10 Quarantine Procedure: Animals will be quarantined for at least 3 days, from receipt until dosing is initiated on day 6 of gestation. During the quarantine period the animals will be observed daily for signs of illness and all unusual observations will be reported to the Study Director, Toxicologist or Veterinarian. Animals will be examined during quarantine and approved for use by the veterinarian prior to being placed on test. Any sickly animal will be either eliminated prior to the test animal selection process or replaced by a healthy animal following this procedure but prior to initiation of treatment under the direction of the Study Director or Toxicologist. Quarantine release will be documented on the Clinical Veterinarian Log by a veterinarian prior to study initiation.

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Contract No.: DAMD17-92-C-2001
Task Order No.: UIC-13D
Study No.: 173

- 7.11 Food: The animals will be fasted on the day of arrival. They will receive approximately 25 g of High Fiber Certified Rabbit Chow #5325 (PMI Feeds, Inc., St. Louis, MO) on the second day, which will be gradually increased over a few days to approximately 100-130 g/day. This regimen is recommended by the animal supplier (HRP, Inc.) to reduce the incidence of intestinal problems. On the days of measured food consumption, an exact amount of 130 g will be provided.
- 7.12 Water: Tap water from an automatic watering system in which the room distribution lines are flushed daily will be provided *ad libitum* from arrival until termination. The water is untreated with additional chlorine or HCl.
- 7.13 There are no known contaminants in the feed or water which are expected to influence the study. A copy of the feed certification will be kept with the study records. The results of the most current comprehensive chemical analyses of Chicago water are documented in files maintained by Quality Assurance.
- 7.14 It is not known if the animals will experience pain or distress during the study. Analgesic or anesthetic agents will confound the ability to determine the toxic potential of the test article, and therefore will not be used. If an animal is in severe pain or distress, following consultation with the veterinary staff, it will be euthanized in accordance with standard operating procedures.

8.0 EXPERIMENTAL DESIGN:

8.1 Treatment Groups:

<u>Group No.</u>	<u>Treatment</u>	<u>Dose Level</u> (mg base/kg/day)	<u>Number of</u> <u>Females*</u>
1	Vehicle	0	20
2	WR6026•2HCl	3	20
3	WR6026•2HCl	7	20
4	WR6026•2HCl	15/10***	20
5**	Vitamin A (Retinol Palmitate)	75,000 IU/kg/day (300 mg/kg/day)	20

* Presumed pregnant

** The positive control agent was administered orally at the specified dose on days 9 and 10 of gestation at a dosing volume of 1 ml/kg.

*** The high dose was reduced from 15 mg base/kg/day to 10 mg base/kg/day on gestation days 12 - 15 (the range of days reflects study stagger-start over 4 days).

Dose levels were selected on the basis of a range-finding study (UIC/TRL Study No. 172). The number of animals, 20/dose level, is the number of animals required by the 1966 FDA Guidelines for Reproduction Studies for Safety Evaluation of Drugs for Human Use (Goldenthal Guidelines), and is the number of animals indicated by the Sponsor in Task Order UIC-13.

- 8.2 Frequency and Route of Administration of Test Article: The test article will be administered once daily by gavage during the period of major organogenesis, gestation days 6 through 18. It will be given at a dosing volume of 1 ml/kg. The control group will receive the vehicle at the same dosing volume. The specific volume to be administered will be adjusted on the basis of each animal's most recent body weight.
- 8.3 Justification of Route(s): The oral route is a convenient and accepted procedure for administering a specific amount of a test article to each animal. It mimics potential human exposure conditions and is specified by the Sponsor.
- 8.4 Procedure to Control Bias during the Assignment of Animals to Treatment Groups: During the quarantine/pretest period, animals judged to be healthy and meeting acceptable body weight requirements will be assigned to the study at random using a randomization procedure on the basis of body weight.
- 8.5 Test Article Vehicle: Deionized distilled water.
- 8.6 Test Article Dosage Form Preparation and Analyses: The dosage formulations of the test article will be prepared once at the beginning of the study. Stability data obtained from a previous study (UIC/TRL Study No. 091) indicated that dosing solutions are stable for at least 12 days.

The stock test article solutions will be prepared by dissolving the appropriate quantity of test article in the vehicle. All dosing solutions will be stored at 0 - 4°C. Samples of the dosage formulations will be analyzed for test article concentration prior to use. Only samples within 10% of their intended concentration will be used. The dosing solution will be re-analyzed at the end of the dosing period.

- 8.7 Frequency of Observations, Test Analyses and Measurements:
- 8.7.1 Mortality Check: All animals will be observed twice daily, at least six hours apart for moribundity/mortality.
- 8.7.2 Clinical Signs: All animals will be observed daily for clinical signs of toxicity approximately 1-2 hours after dosing (days 6-18), and in the morning after completion of the dosing period (days 19-29). Moribund animals will be sacrificed on that day and the uterine contents will be examined as described in section 8.7.6.
- 8.7.4 Body Weights: Individual body weights will be recorded on day 0 of gestation, at randomization, and on gestation days 6-18, 24 and 29.
- 8.7.5 Food Consumption: Food consumption for all animals will be measured during the following 24 hour intervals: days 7/8, 9/10, 11/12, 14/15, 17/18, 23/24, 28/29.

8.7.6 Sacrifice: On day 29 of presumed gestation, all surviving female rabbits will be killed by intravenous injection of sodium pentobarbital (50 mg/kg) via the marginal ear vein. Any female showing signs of abortion ($GD < 28$) or premature delivery ($GD \geq 28$) will be euthanized on the same day and evaluated as in sections 8.7.7 - 8.7.9.

8.7.7 Cesarean-Sectioning Observations: The abdominal and thoracic cavities will be opened by a ventral midline incision and the contents examined. In gravid animals, the ovaries will be examined. The number of corpora lutea on each ovary will be recorded (ovaries discarded after evaluation). The gravid uterus will be examined and weighed. The number and location of viable and nonviable fetuses* *in utero*, early and late resorptions** and the total number of implantation sites will be recorded.

The uterine position of each fetus will be documented using the following procedure. All implantation sites, including resorptions, will be numbered in consecutive fashion and similarly with the right distal uterine horn, noting the position of the cervix. Maternal tissues will only be saved for histopathological examination in 10% neutral buffered formalin as deemed necessary by the gross findings. The carcass of each dam will then be discarded.

*A viable fetus is defined as one which responds to stimuli. A non viable fetus is defined as a term fetus, which does not respond to stimuli *in utero* or is not breathing.

**An early resorption is defined as one in which it is not grossly evident that organogenesis has occurred. A late resorption is defined as one in which it is grossly evident that organogenesis has occurred. A fetus with evident autolysis is considered a late resorption.

8.7.8 Confirmation of Pregnancy: Uteri from females that appear nongravid will be opened and placed for approximately 10 minutes in ammonium sulfide solution (10%) for detection of possible implantation sites. If any implantation sites are detected, the ovaries will be examined as in 8.7.7.

8.7.9 Necropsy: Rabbits which die will be examined for the cause of death. Rabbits which require termination due to moribund condition will be killed and examined. Necropsy will occur on the same calendar day on which death or termination occurs. Examination will not be performed if precluded by postmortem autolysis. Pregnancy status and uterine contents will be recorded. Maternal tissues with gross lesions appropriate for retention will be fixed in neutral buffered 10% formalin for possible future evaluation. Exception: (Parovarian cysts will be discarded; these are common, spontaneous lesions in rabbits). Viscera which appear normal will be discarded. Naturally-delivered pups will be examined to the extent possible using the same methods described for fetuses.

8.7.10 Fetal Gross Observations: Fetuses will be removed from the uterus and placed in individual containers. After sex and body weights are recorded, each fetus will be individually identified noting litter, uterine placement and study number.

8.7.11 Fetal Morphological Examination:

8.7.11.1 External: A detailed examination of each fetus will be conducted to include the eyes, palate, trunk and extremities. Any abnormal finding will be recorded. Late resorptions will be recorded and the tissue discarded or kept in formalin 10% as deemed necessary by the Study Director or the Reproductive Toxicologist.

8.7.11.2 Visceral Evaluation: All live fetuses will be examined for visceral anomalies and will be sexed internally employing the Staples' fresh tissue dissection techniques (Staples, 1974). All fetuses will be euthanized by I.P. injection of 40% solution of sodium pentobarbital (0.4 ml/fetus). Fetal examination will include evaluation of the eyes and the brain by a mid-sagittal section. The remaining carcass will be retained in 95% ethyl alcohol.

8.7.11.3 Skeletal Evaluation: Following completion of the visceral examination, all fetuses will be eviscerated and skinned for subsequent staining with Alizarin Red S for evaluation of the fetal skeletons (Dawson, 1926). Skeletal preparations will be stored in 99.5% glycerin and 0.5% phenol and will be retained.

8.7.12 Statistical Analyses: Maternal body weights, weight gains, absolute uterine weight, and fetal body weights will be analyzed by a one-way analysis of variance. If a significant F ratio is obtained ($p \leq 0.05$), Dunnett's test will be used for pair-wise comparisons to the control group.

The incidence of fetal abnormalities will be examined in terms of the fetal and litter percentages (% abnormal fetuses/group & % abnormal letters/group). Abnormalities will include malformations in addition to variations. The proportions of litters with abnormalities and male to female fetal sex ratios will be compared by using the Chi-square test criterion with Yate's correction for 2 x 2 contingency tables and or Fisher's exact probability test.

Maternal food consumption data, the numbers of resorptions, non viable fetuses, viable fetuses, *corpora lutea*(C.L.), implantations, preimplantation loss*, postimplantation loss** and total implantation loss*** will be compared using the Kruskal-Wallis test. If a significant effect is seen ($p \leq 0.05$), the Mann-Whitney U test will be used for pair-wise comparisons to the control group.

*Preimplantation loss % = $[(\#C.L. - \#implantations)/\#C.L.] \times 100$

**Postimplantation loss % = $[(\#implantations - \#live\ fetuses)/\#implantation] \times 100$

***Total implantation loss % = $[(\#C.L. - \#live\ fetuses)/\#C.L.] \times 100$

Other statistical analyses will be conducted as deemed necessary and will be documented in the raw data.

Only appropriate data from pregnant animals will be included in the evaluation or the statistical analysis. In animals with abortion or premature delivery, uterine weight and fetal body weights and sexes will not be included in the statistical analysis.

In addition to the written report, summary data tables of parameters and variability will be transmitted to the Sponsor on magnetic media (computer diskette) in "ASCII" form. The transcribed data on disk will no longer be considered GLP compliant.

9.0 RECORDS TO BE MAINTAINED:

All data generated during the conduct of the study, except those that are generated as direct computer input, shall be recorded directly, promptly, and accurately in ink in bound books with prenumbered pages or on worksheets that shall be bound during or at the conclusion of the nonclinical laboratory study. All appropriate computer and machine output shall be bound during or at the conclusion of the study. All data entries shall be dated on the day of entry and signed or initialed by the person entering the data.

Any changes in entries for whatever reason (e.g., to correct an error or transposition) shall be made so as not to obscure the original entry, shall indicate the reason for such change, and shall be dated and signed or identified at the time of data input. In computer driven collection systems, the operator responsible for direct data input shall be identified at the time of data input. Any changes in computer entries for whatever reason (e.g., to correct an error or transposition) shall be made in such a manner so as not to obscure the original entry, if possible, shall indicate the reason for such change, and shall be dated by the responsible individual.

All recorded data shall be reviewed, signed, and dated by a knowledgeable person, other than the person making the entry, to assure adherence to procedures and to verify observations.

Upon completion of the study and submission of the final report, all raw data, documentation, specimens, test article reserves and other materials necessary to reconstruct the study will be stored in the TRL archives maintained by Quality Assurance.

All changes or revisions, and reasons therefore, to this protocol once it is approved shall be documented, signed by the Study Director and Sponsor, dated and maintained with the protocol.

10.0 REGULATORY REQUIREMENTS:

This study will be performed in compliance with the UIC/TRL Quality Assurance Program designed to conform with FDA Good Laboratory Practice Regulations and EPA Good Laboratory Practice Standards.

Will this study be submitted to a regulatory agency? Yes If so, to which agency(ies)? Food and Drug Administration

Does the Sponsor Request that remaining test article be returned? Possibly: direction will be provided by the Sponsor.

Does the Sponsor request that samples of the test article/carrier mixture(s) be returned to the Sponsor? No

DRAFT

11.0 REFERENCES:

Dawson, AB (1926). A note on the staining of cleared specimens with Alizarin Red S. Stain Technol. 1:123-124.

Dunnett, CW (1955). A multiple comparison procedure for comparing several treatments with a control. J. Amer. Stat. Assoc. 50:1096-1129.

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Hayes, W (1989). Principles and Methods of Toxicology, pp 311-361, Raven press. New York, NY.

HRP, Inc. Rabbit quality and consistency. HRP NZW time-mated conception rates. (9/3/92).

Kimmel, CA and Trammell, C (1981). A rapid procedure for routine double staining of cartilage and bone in fetal and adult animals. Stain Technol. 56: 271-273

Snedecot, GW and Cochran, WG (1967). Variance test for homogeneity of the binomial distribution. Statistical Method, 6th Edition, pp. 240-241, Iowa State University Press. Ames, IA.

Staples, RE (1974). Detection of visceral alterations in mammalian fetuses. Teratol. 9: A-37.

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REVISED PAGE	
STUDY NO: 173	INITIAL: <i>PL</i>
DATE: 3/27/95	

DRAFT

Contract No.: DAMD17-92-C-2001
Task Order No.: UIC-13D
Study No.: 173

U.S. Environmental Protection Agency (1991). Guidelines for developmental toxicity risk assessment. Notice. Fed. Regist. 56: 63798-63826.

U.S. Food and Drug Administration (1966). Guidelines for reproduction studies for safety evaluation of drugs for human use.


Wilson, JG (1965). Methods for administering drugs and detecting malformations in experimental animals. *In*: Teratology Principles and Techniques (Wilson, J.G. and Warkany, J., eds.). pp. 262-277, Un. Chicago Press. Chicago, IL.

DRAFT

Contract No.: DAMD17-92-C-2001
Task Order No.: UIC-13D
Study No.: 173


12.0 PROTOCOL APPROVAL:

STUDY DIRECTOR:


Barry S. Levine, D.Sc., D.A.B.T.

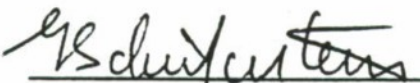
7/5/94
Date

QUALITY ASSURANCE:


Ronald Schoenbeck

7/5/94
Date

SPONSOR APPROVAL:


George J. Schleferstein, Ph.D.
Contracting Officer's
Representative (COR)

7/6/94
Date

COMMENTS FROM THE COR:

Office of the Vice Chancellor for Research (M/C 672)
310 Administrative Office Building
1737 West Polk Street
Chicago, Illinois 60612-7227
(312) 996-4995

DRAFT

APPENDIX 1

July 13, 1994

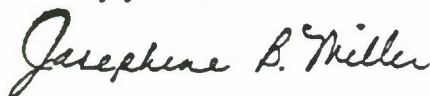
Barry S. Levine
Pharmacology
312 BGRC, M/C 868

Dear Dr. Levine:

The modifications requested in your correspondence of July 7, 1994 pertaining to your approved protocol ACC 93-077-15: "Developmental Toxicity (Segment II) Study of WR6026 Dihydrochloride in Rabbits" have been reviewed in accordance with the Animal Care and Use Policies of the University of Illinois at Chicago. You will be pleased to know that the modifications were approved on July 13, 1994 and consequently the records of Animal Care Committee will be revised to reflect these changes.

Thank you for complying with the Animal Care Policies and Procedures of UIC.

Sincerely yours,



Josephine B. Miller, Ph.D.
Chair, Animal Care Committee

JBM:st
xc:BRL

Study No.: 173

Title: Developmental Toxicity (Segment II) Study of WR6026 Dihydrochloride in Rabbits

1. Page 1 Section 4.0

Add the following dates:

Proposed Initiation of In-life Phase (Day 0): 03/07/95

Proposed Completion of In-life Phase: 04/07/95

Proposed Study Completion Date
(Draft Final Report): 07/07/95

Reason: Dates were not finalized when the protocol was submitted.

2. Page 2 Section 5.1

Correct base molar fraction to 0.825.

Reason: Typographical mistake.

3. Page 2 Section 6.0

Add the following to personnel

Lead Technician Nancy Dinger, B.S.

Reason: To indicate proper personnel.

4. Page 4 Section 7.11

In the second sentence delete "Purina".

Reason: To reflect the correct name.

Study No.: 173

Title: Developmental Toxicity (Segment II) Study of WR6026 Dihydrochloride in Rabbits

5. Page 4 Section 8.1

A. The following doses were assigned to Groups 1-5:

<u>Group No.</u>	<u>Treatment</u>	<u>Dose Level</u> <u>(mg base/kg/day)</u>
1	Vehicle	0
2	WR238605 Succinate	3
3	WR238605 Succinate	7
4	WR238605 Succinate	15
5	Vitamin A (Retinol Palmitate)	75,000 IU/kg/day (=300 mg/kg/day)

B. Change "will be" to "were" in the first sentence of the paragraph.

Reason: A. The doses of the test article have now been determined and the teratogenic dose in rabbits of Retinol Palmitate was reduced based on preliminary studies performed by TRL.

B. To reflect that the dose range-finding study has been done, from which dose levels were chosen.

6. Page 5 Section 8.7.4

Change gestation days for body weight measurements to days 6-18, 24 and 29.

Reason: Change in procedure.

7. Page 6 Section 8.7.6

Add the following sentence to the end of the section "Any female showing signs of abortion (GD < 28) or premature delivery (GD ≥ 28) will be euthanized on the same day and evaluated as in sections 8.7.7 - 8.7.9"

Reason: To clarify the procedure.

8. Page 6 Section 8.7.7

Replace the sentence "and continuing from the proximal to distal right uterine horn" by the sentence "and similarly with the right distal uterine horn, noting the position of the cervix."

Study No.: 173

Title: Developmental Toxicity (Segment II) Study of WR6026 Dihydrochloride in Rabbits

Reason: To clarify the procedure.

9. Page 6 Section 8.7.8

Change the ammonium sulfide solution concentration from 0.5% to 10%.

Reason: To match the Pathology Associates, Inc., standard operating procedure.

10. Page 7 Section 8.7.11.2

Replace the section after the first sentence to read as follows:

All fetuses will be euthanized by I.P. injection of 40% solution of sodium pentobarbital (0.4 ml/fetus). Fetal examination will include evaluation of the eyes and the brain by a mid-sagittal section. The remaining carcass will be retained in 95% ethyl alcohol.

Reason: To clarify the procedure.

11. Page 7 Section 8.7.11.3

Change the end of the first sentence to read "...subsequent staining with Alizarin Red S for evaluation of the fetal skeletons (Dawson, 1926). Skeletal preparations will be stored in 99.5% glycerin and 0.5% phenol and will be retained".

Reason: Alizarin Red S is a preferred technical method with similar evaluation efficiency to the double staining method and is less time consuming. The phenol is added to prevent molding.

12. Page 7 Section 8.7.12

Replace the statistical analysis section by the following:

Maternal body weights, weight gains, absolute uterine weight, and fetal body weights will be analyzed by a one-way analysis of variance. If a significant F ratio is obtained ($p \leq 0.05$), Dunnett's test will be used for pair-wise comparisons to the control group.

Study No.: 173

Title: Developmental Toxicity (Segment II) Study of WR6026 Dihydrochloride in Rabbits

The incidence of fetal abnormalities will be examined in terms of the fetal and litter percentages (% abnormal fetuses/group & % abnormal litters/group). Abnormalities will include malformations in addition to variations. The proportions of litters with abnormalities and male to female fetal sex ratios will be compared by using the Chi-square test criterion with Yate's correction for 2 x 2 contingency tables and or Fisher's exact probability test.

Maternal food consumption data, the numbers of resorptions, non viable fetuses, viable fetuses, *corpora lutea* (C.L.), implantations, preimplantation loss*, postimplantation loss** and total implantation loss *** will be compared using the Kruskal-Wallis test. If a significant effect is seen ($p \leq 0.05$), the Mann-Whitney U test will be used for pair-wise comparisons to the control group.

*Preimplantation loss % = $[(\#C.L. - \#implantations) / \#C.L.] \times 100$

**Postimplantation loss % = $[(\#implantations - \#live\ fetuses) / \#implantations] \times 100$

***Total implantation loss % = $[(\#C.L. - \#live\ fetuses) / \#C.L.] \times 100$

Other statistical analyses will be conducted as deemed necessary and will be documented in the raw data.

Only appropriate data from pregnant animals will be included in the evaluation or the statistical analysis. In animals with abortion or premature delivery, uterine weight and fetal body weights and sexes will not be included in the statistical analysis.

Reason: To represent more accurately the statistical analysis procedures.

13. Page 9 Section 11.0

Delete Lang LP (1993) reference.

Reason: Irrelevant to the study.

STUDY DIRECTOR


Barry S. Levine, D.Sc., D.A.B.T.

3/27/95
Date

SPONSOR APPROVAL


George J. Schieferstein, Ph.D.

4/4/95
Date

PROTOCOL AMENDMENT

Study No.: 173

Title: Developmental Toxicity (Segment II) Study of WR6026 in Rabbits

14. Page 4 Section 8.1

- 1) Change the high dose level from 15 to 15/10***
- 2) Add the following footnote to the end of the section

***The high dose was reduced from 15 mg base/kg/day to 10 mg base/kg/day on gestation days 12 - 15 (the range of days reflects study stagger-start over 4 days).

Reason: Due to the observed fatalities in 3 females preceded by manifest cyanosis and rapid respiration and since cyanosis was also observed in most of the high dose females, reduction of the dose was aimed to reduce the number of losses among the high dose group.

STUDY DIRECTOR


Barry S. Levine, D.Sc., D.A.B.T.

5/1/95
Date

SPONSOR APPROVAL


George J. Schieferstein, Ph.D.

5/2/95
Date

PROTOCOL AMENDMENT

DRAFT

Study No.: 173

Title: Developmental Toxicity (Segment II) Study of WR6026 Dihydrochloride in Rabbits


15. Page 4 Section 8.1

Correct the name of the test article in Groups 2-4 as follows:

<u>Group No.</u>	<u>Treatment</u>	<u>Dose Level</u> <u>(mg base/kg/day)</u>
2	WR6026•2HCl	3
3	WR6026•2HCl	7
4	WR6026•2HCl	15/10***

Reason: Typographical error in the name of the test article.

STUDY DIRECTOR:


Barry S. Levine, D.Sc., D.A.B.T.

6/24/95
Date

SPONSOR APPROVAL:

George J. Schieferstein, Ph.D.

Date

DRAFT

APPENDIX 7

Study Deviations

DRAFT

DEVELOPMENTAL TOXICITY (SEGMENT II)
STUDY OF WR6026 DIHYDROCHLORIDE IN RABBITS

Study Deviations*

<u>Deviation Type</u>	<u>Specific Deviation</u>	<u>Effect on Study</u>
Protocol	Five females in the positive control group received their second dose on GD12 instead of GD10.	None, since similar anomalies to those dosed on GD10 were observed.
Protocol	One high dose female was not necropsied after found dead on GD15.	None, since limited C-section data from found dead animals are used in the statistical analysis.
Protocol	The animal room temperature was out of range on several occasions.	None, deviations were minimal.

*The detailed "Deviation Reports" are contained in the raw data which are archived at the Toxicology Research Laboratory, University of Illinois at Chicago, Department of Pharmacology, 1940 W. Taylor St., Chicago, IL 60612.

The above deviations did not affect the integrity of the study.

Barry S. Levine, D.Sc., D.A.B.T.

Date